SUMMARY OF RESEARCH UNDER NASA GRANT NGL 14-001-012, SEPTEMBER, 1969 to DECEMBER, 1970

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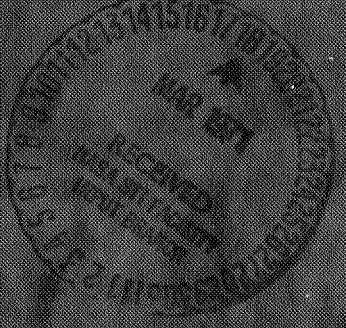
The Department of Biophysics
The University of Chicago



SUMMARY OF RESEARCH UNDER NASA GRANT NGL 14-001-012 DURING THE PERIOD FROM SEPTEMBER, 1969 TO DECEMBER, 1970.

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During the period between September, 1969 and December, 1970, we have been engaged in the following research:

1. Important progress has been made in the examination of lunar material from the Apollo 11 and Apollo 12 missions, using our improved diamond knife sectioning and high voltage electron microscopy techniques.

Our examinations of pyroxenes from Apollo 11 sample 10044-25 revealed uniform bands parallel to (001) which correspond to single crystal domains. The bands occur predominantly in iron-rich crystals and their widths vary from approximately 100Å to 600Å. Mössbauer spectra of the iron-rich crystals revealed magnetic hyperfine splitting at low temperatures, and we were able to consider correlation of the band structures with possible magnetic ordering.

Separates of yellow-green pigeonite $En_{60}Fs_{33}Wo_7$ described by our colleagues Drs. David Virgo and Stefan S. Hafner from Apollo 12 sample 12021,150 were examined by transmission electron microscopy and diffraction in a tilting stage at 75 kV, 100 kV and 200 kV with specimen cooling at 1.85°K, 4.2°K and at room temperature.

Light and dark field micrographs show uniform dense bands about 200Å wide oriented along (001) and additional bands oriented along different planes. Correlated electron optical and crystallographic studies of other lunar clinopyroxenes and terrestrial reference specimens are being carried out under controlled experimental conditions as an aid to interpreting the origin of the pyroxene substructure and the geophysical significance of the available data.

2. The installation of a Collins closed-cycle superfluid helium refrigeration unit and its repeated operational success in supplying the high voltage microscope cryo-stat with liquid helium at temperatures of 1.85°K has provided us with a major breakthrough in this field. At the 7th International Electron Microscope Congress in Grenoble last summer, our work in this area was well-received by the distinguished participants, and my discussions with those attending the meeting make it possible for me to say with all confidence that our unique high voltage cryo-electron microscope is the only one of its kind now operational in the world.

Recently, we have observed a prolonged self-sustaining property in the superfluid helium within the microscope cryo-stat. This has permitted us to record some unusually high quality micrographs of the specimens under study, revealing the increased stability and the significantly decreased radiation damage which examination at such

low temperatures allows. The importance of this may be demonstrated in the significance of lossless transmission of energy for meeting the mounting problems of critical power shortages.

3. We are continuing our development of high-resolution electron-optical information storage and retrieval systems. We have been able to demagnify both halftone and color printed images by factors of 1:500 to 1:1000 using the coherent electron microbeam. The images are recorded on special emulsions and recording films in which silver has been replaced with aluminum, thereby significantly reducing the cost of the film in comparison with conventional recording films now commercially available.

Using a special plastic high pressure molding process, ultra-violet transmitting plastic and precision molds generated by a computer-controlled process, we can produce about 400 to 1600 plastic high resolution lenses per square inch. These lenses are of short focal length and both the aspherical and spherical types. Our own high resolution phase contrast microscopy, interferometry and electron optical testing procedures have shown that these lenses are of exceptionally high quality and demonstrate a resolving power superior to any glass lens now available (i.e. 500 to 1000 lines per millimeter).

These same lenses could be incorporated into a small portable projector much like the prototype of the pico-projector which we have developed and are now testing, and since each lens would cost only a fraction of a penny, the entire system could be produced inexpensively.

Interest in the new types of ultra-miniaturized components and the pico-projectors for information storage and retrieval is at an unprecedented level. Some of the "spin-offs" of this work are already becoming manifest. We have recently completed an integrated pico-projector system for the 90-Day Space Station Simulator Test, which we furnished on a loan basis to McDonnell Douglas Astronautics Company, Western Division. This project is under the sponsorship of the National Aeronautics and Space Administration's Langley Research Center at Hampton, Virginia. It was our pleasure to provide the projector on a loan for this project without any remuneration, in keeping with our policy of assisting NASA projects in any way we can. This may well open the way for widespread application of the pico-projector in lunar exploration and related fields.

During the 7th International Electron Microscope Congress, I was privileged to hear discussions on important new techniques in ultra-miniaturization for information storage and retrieval. I was greatly impressed by the substantial lead in this field now held by Japan, Germany, France, England and Holland. The work of researchers in these countries is significantly more advanced than any now being carried out under the auspices of the U.S. government.

Conclusion:

We strongly feel that this promising work should be continued, because these particular studies will ultimately enable us to examine both terrestrial and extra-terrestrial material under conditions approaching the lunar and space environments (i.e. ultra-high vacuums, cryogenic temperatures, etc.). It is generally recognized that cryo-electron microscopy, which was pioneered and developed in our laboratory, probably represents one of the most important advances in the field of ultrastructure research.

December 15, 1970

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High voltage electron microscopy and electron diffraction of lunar pyroxenes

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Abstract—Pyroxenes from lunar rock 10044-25, cleaved and sectioned by diamond knife ultramicrotomy were examined by standard and high voltage electron microscopy and diffraction.

Salient findings based on the evaluation of 2000 plates show uniform bands parallel to (001) which correspond to single crystal domains. The bands occur predominantly in iron-rich crystals and their widths vary from approximately 100 Å to 600 Å.

Mössbauer spectra of the iron-rich crystals reveal magnetic hyperfine splitting at low temperatures. Correlation of the band structure with possible magnetic ordering is considered.

INTRODUCTION

IN VIEW of the unusual variations in chemical composition which have been observed in many crystals of lunar pyroxene (cf. *Science* **167,** in particular the section on General Mineralogy) and of the exsolution phenomena occasionally observed in terrestrial and meteoritic pyroxenes (BOYD and BROWN, 1969; BINNS *et al.*, 1963; DUKE and SILVER, 1967), combined electron microscope and electron diffraction studies were carried out. In this paper we report some interesting observations on the fine structure in pyroxenes from a Type B lunar igneous rock (microgabbro) and some preliminary electron diffraction data.

EXPERIMENTAL

Clinopyroxenes from Apollo 11 sample 10044-25 were crushed to a grain size of about 50 μ and were further separated into distinct Mg, Fe, Ca compositions (10044-25-P2; 10044-25-P3).

The crystals were fragmented or cleaved and sectioned using diamond knives and a special ultramicrotome of the Fernández-Morán type (FERNÁNDEZ-MORÁN, 1953; 1956a, b). The pyroxene specimens were mounted without support or after embedding in epoxy. The exceptionally uniform 2·5 mm–4·0 mm diamond cutting edge of molecular dimensions was essential to the production of serial sections about 100 Å–400 Å thick (Fig. 1a) for transmission electron microscopy.

The resulting highly polished surfaces (Fig. 1b) of the pyroxene crystals with cross-sections of several square millimeters are also suitable for preparation of replicas and pseudoreplicas.

The specimens were mounted directly on ultra-thin carbon films or fenestrated platinum and copper grids taking rigorous precautions to avoid water or solvent contamination in a clean room atmosphere.

Specimens were examined by both standard (50–100 kV) and high voltage (200 kV) electron microscopy and selected-area electron diffraction techniques (FERNÁNDEZ-MORÁN, 1966, 1967). Significant advantages of the high voltage Hu-200E microscope include higher penetration power, reduced radiation damage, enhancement of structural detail in thick specimens and increased diffraction accuracy. Some results from the evaluation of approximately 2000 plates are given in the following section.

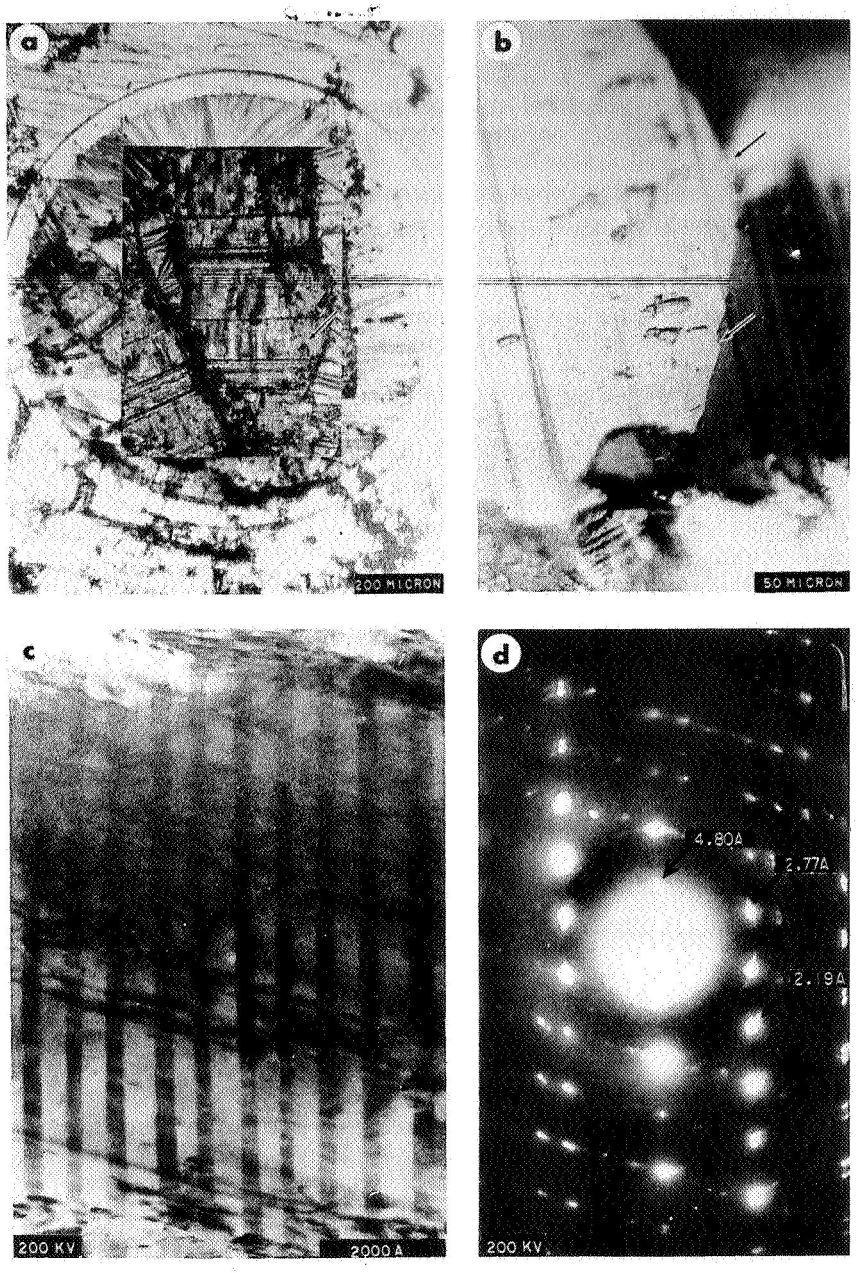

Fig. 1. (a) Ultrathin layer of pyroxene sectioned with diamond knife and mounted on electron microscope grid. (b) Surface of pyroxene crystal prepared by diamond knife ultramicrotomy. (c) High voltage electron micrograph of lunar pyroxene 10044-25 showing regular band structure. (d) Selected-area electron diffraction pattern of pyroxene 10044-25.

Results and Discussion

Pyroxene crystals from rock 10044 exhibit exceptionally regular and periodically spaced, dense bands which are oriented parallel to (001). The widths of the bands range from 100 Å to 600 Å (Figs. 1–7) with an average of about 300 Å. The distribution is shown in the histogram of Fig. 2. These bands often appear straight-edged

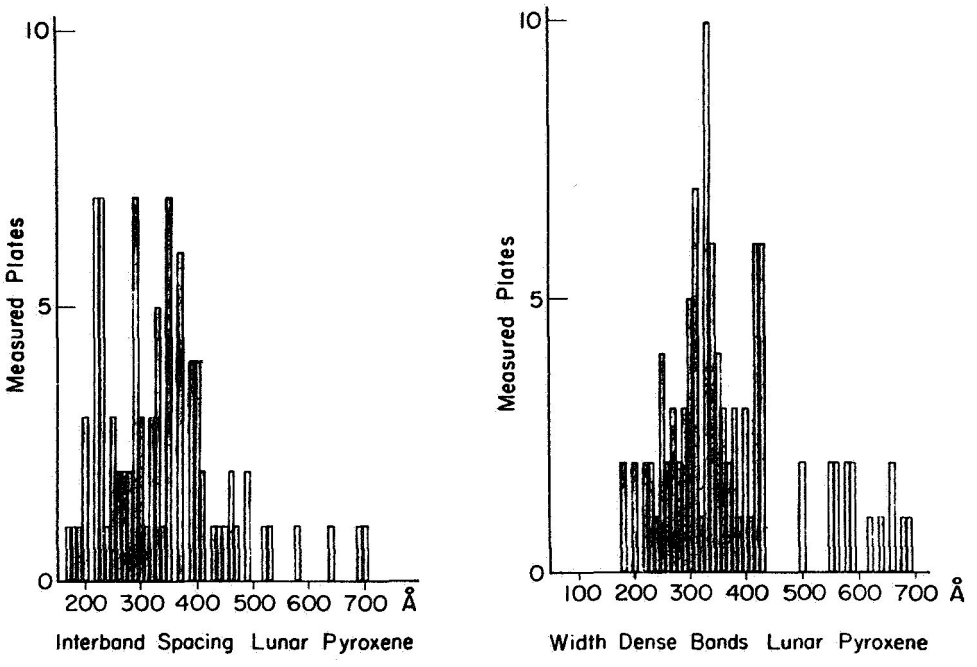

Fig. 2. Histograms of dense band widths and interband spacings in pyroxene 10044-25.

and have exceptionally sharp boundaries even at the highest magnifications. The sharpness of the boundaries is strikingly similar to images of magnetic domain walls as seen in thin layers of ferromagnetic materials (Silcox, 1963). The bands are distinctly seen in both bright and dark field illumination (Figs. 3, 4). Although the electron density within the bands is generally uniform, a mosaic pattern is displayed in certain distorted areas, especially under high electron beam illumination. It should be noted that the bands occur predominantly in iron-rich crystals 10044-25-P3 (Hafner and Virgo, 1970, Tables 1, 2). Sharp bands seem to be absent in the magnesium-rich separate 10044-25-P2. Instead, the latter show irregular striations along the cleaved planes (Figs. 5b, 5d). Dense granules (ca. 100 Å–1000 Å in dia.) are also found in iron-rich crystals (Fig. 5a).

The bands exhibit electron optical phenomena corresponding to single-crystal domains as shown by selected-area electron diffraction patterns (Fig. 6). By a combination of high-resolution dark field electron microscopy with the selected-area electron diffraction technique, intrinsic lattice spacings of 2·5 Å could be detected within the bands, probably corresponding to d(200) as illustrated in Figs. 6a, 6b, 6c, 6d.

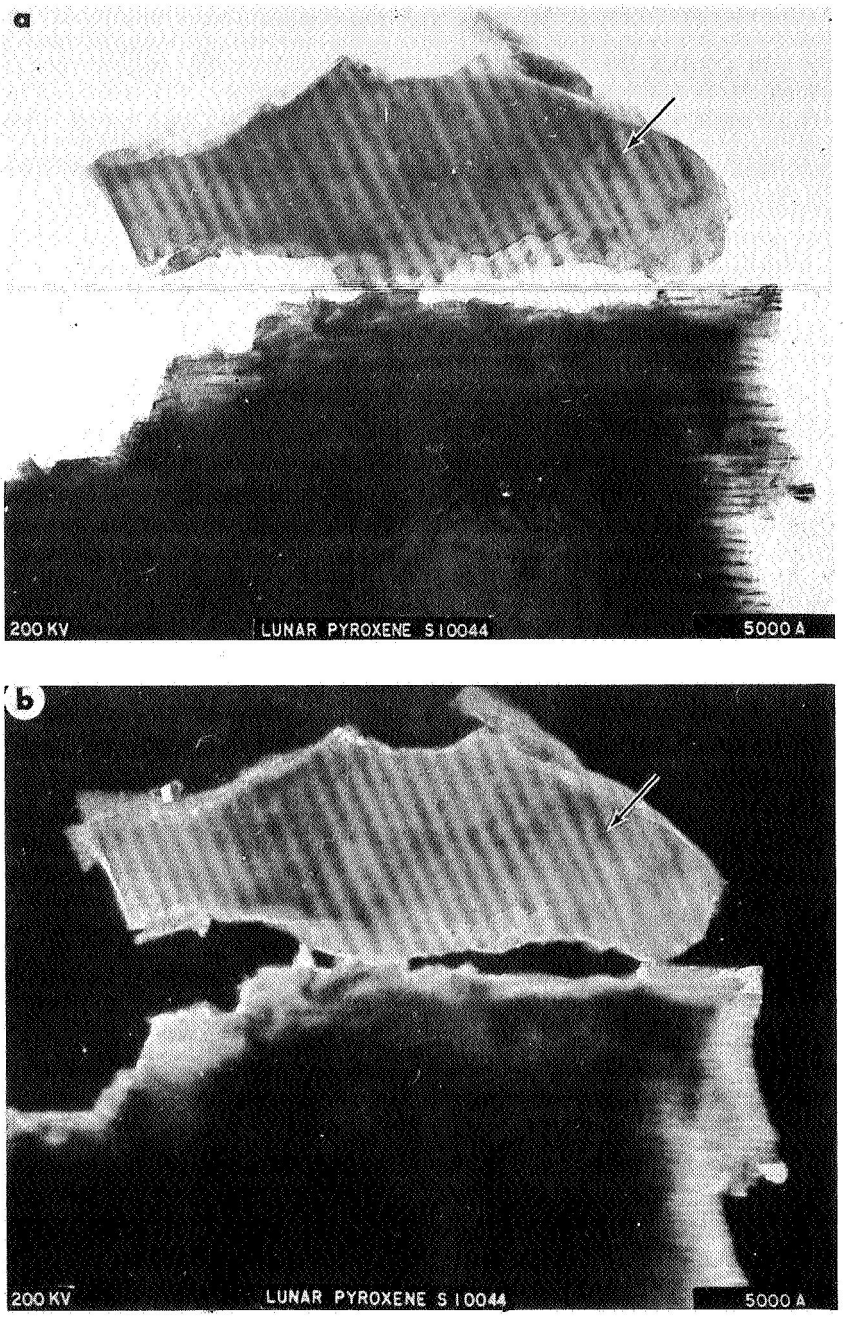

Fig. 3. High voltage electron micrographs of cleaved pyroxene 10044-25 showing (a) bright field and (b) dark field images of band structure.

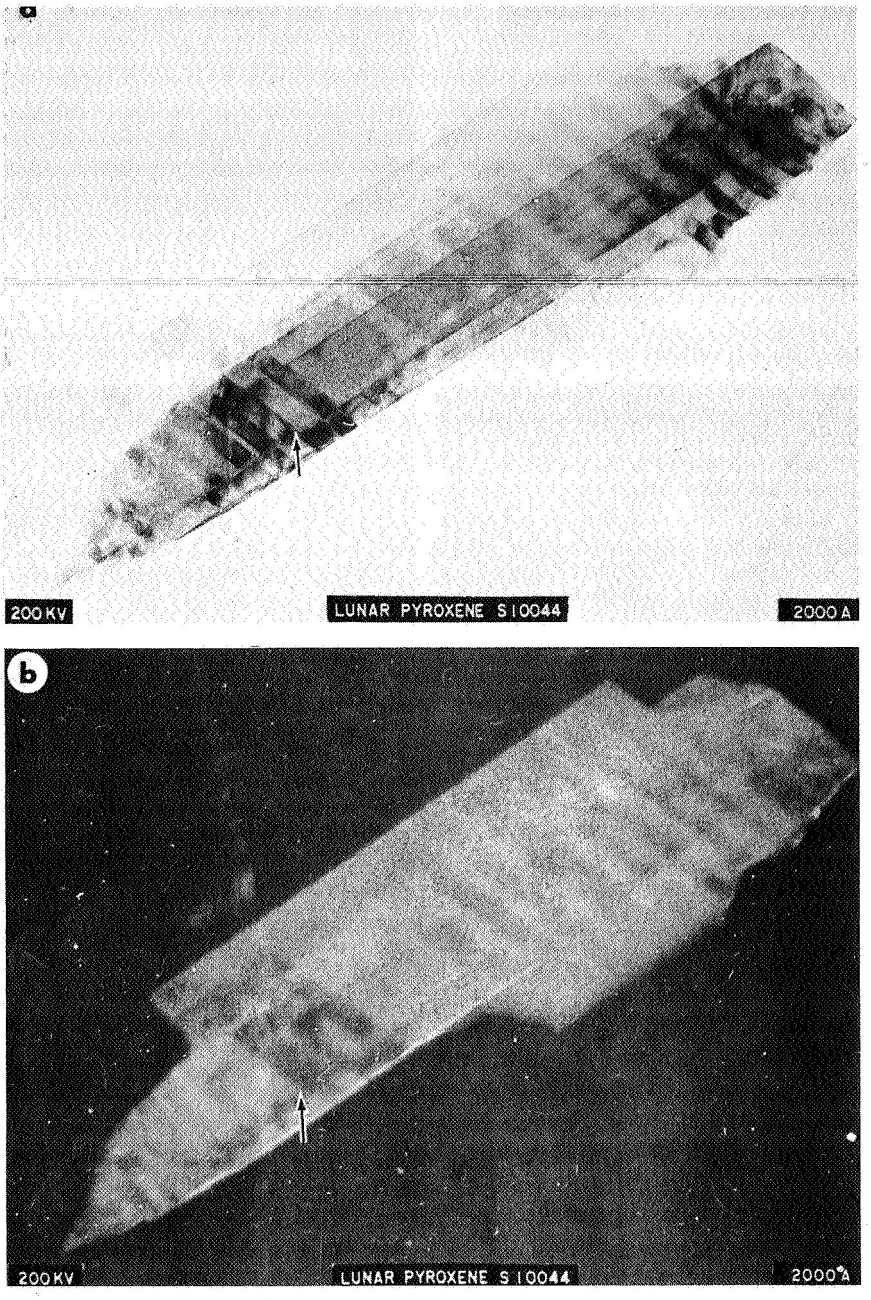

Fig. 4. High voltage electron micrographs of cleaved pyroxene 10044-25-P3 showing (a) bright field and (b) dark field images of bands oriented parallel to (001).

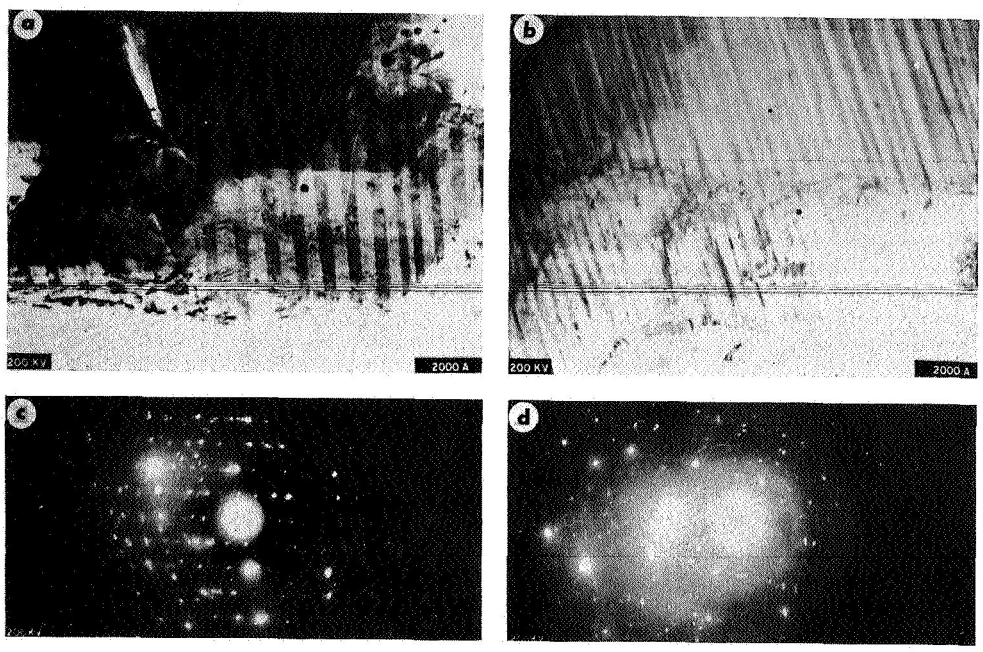

Fig. 5. High voltage electron micrograph (a) and selected-area diffraction pattern (c) of iron-rich pyroxene 10044-25-P3 showing uniform dense bands and irregular granules compared with magnesium-rich pyroxene 10044-25-P2 crystalline layers (b, d) exhibiting irregular striations.

Lattice spacings of 6·5 Å were directly visualized in high resolution bright and dark field images which could be compared with corresponding electron diffraction patterns (Figs. 7d).

The characteristics of the lamellar structure in the lunar pyroxene as described above is consistent with similar observations of BAILEY *et al.* (1970), ROSS *et al.* (1970), and RADCLIFFE *et al.* (1970). It can be interpreted as an exsolution phenomenon during the cooling history subsequent to crystallization. More complex processes, however, should also be considered. ROSS *et al.* (1970), for example do give evidence of a more complex process since they suggest partial intragranular recrystallization of pigeonite and augite within originally large subcalcic augite crystals.

The regularly striped band patterns occur over rather large areas and the small size of their band widths is unusual. A possible explanation for the small size of the domains might be the comparatively small concentration of protons in the lunar igneous rocks which may have hindered cationic migration between crystal boundaries or over large distances within the crystals. Significant amounts of coarser exsolution lamellae were not observed either with light microscopy or electron microprobe analysis (cf. BAILEY *et al.*, 1970; KEIL *et al.*, 1970; ROSS *et al.*, 1970).

Typical examples of exsolution are calcium-rich lamellae in orthopyroxenes which have bulk compositions close to the system (Mg, Fe)SiO_3. We have examined crystals of orthopyroxene XYZ which are known to be chemically homogeneous but

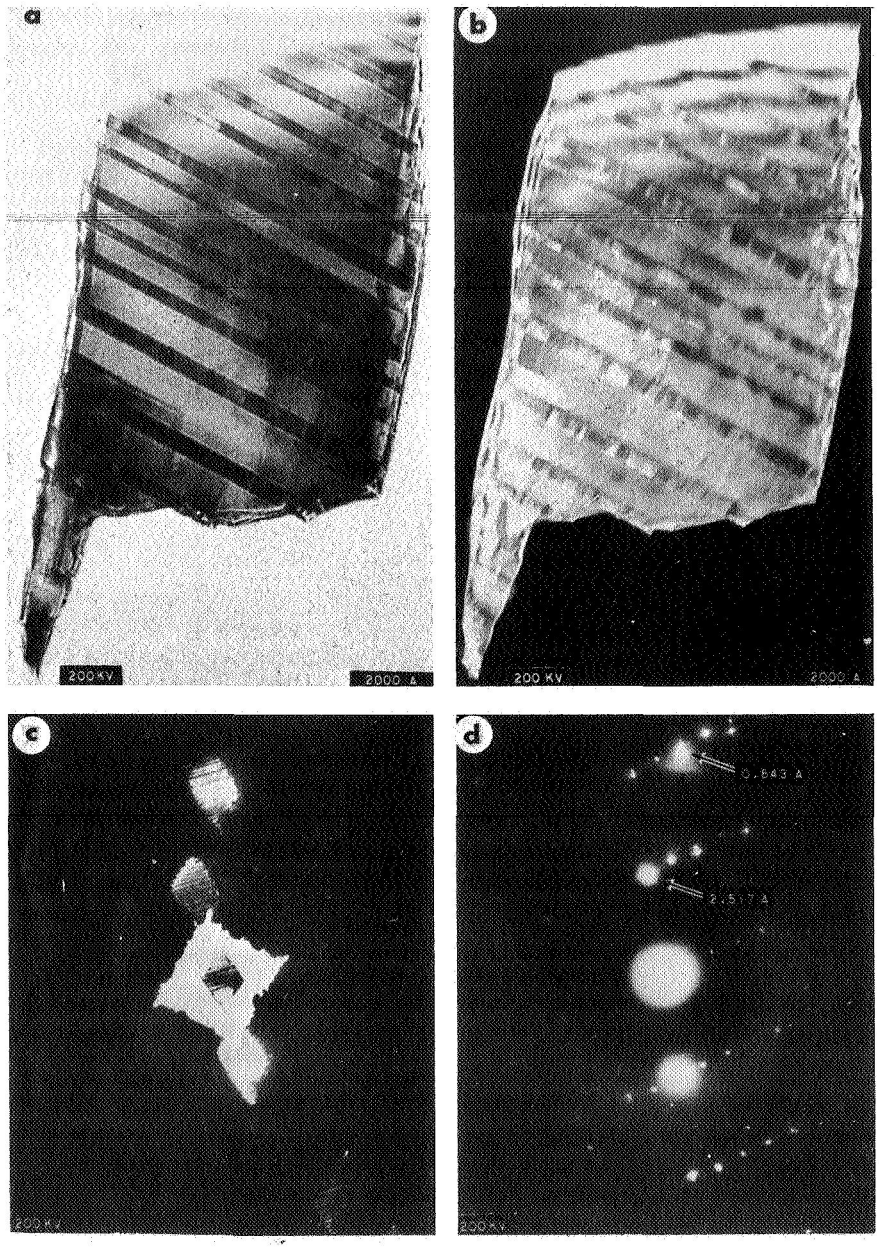

Fig. 6. High voltage electron micrographs of pyroxene 10044-25 showing (a) bright field and (b) dark field images of dense band structure with corresponding selected-area diffraction patterns (c, d).

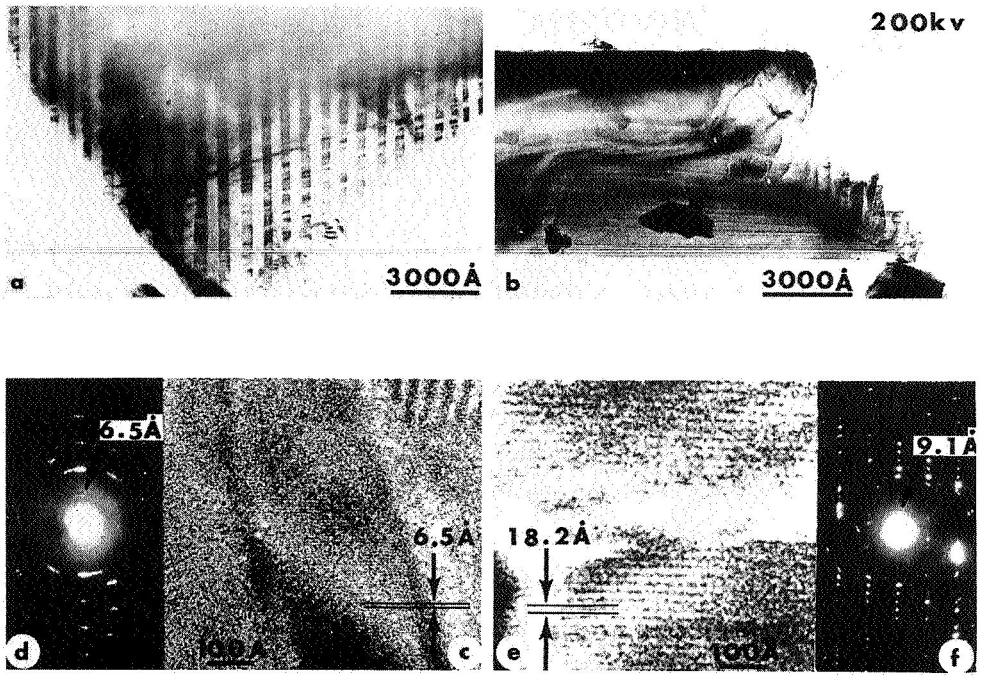

Fig. 7. High voltage electron micrographs of cleaved pyroxene showing (a) dense band structure of pyroxene 10044-25-P3 and (b) layer structure of pyroxene XYZ. High resolution electron micrograph (c) and selected-area diffraction pattern (d) of pyroxene 10044-25-P3 compared with corresponding images of pyroxene XYZ (e, f).

do contain 4 atomic per cent calcium. In this particular case no bands or other fine structures were detected (Fig. 7b). This is indicative of a dilution of calcium in the orthopyroxene single crystal. In XYZ crystals 18·2 Å spacings which may be correlated with a_0 were directly visualized (Fig. 7e).

Mössbauer resonant absorption studies of ^{57}Fe in the iron-rich specimen 10044-25-P3 at liquid helium temperatures revealed magnetic hyperfine splitting. A relatively sharp transition temperature exists between 20°K and 30°K, which can be interpreted as a Néel point. The spin orientations below this point are assumed to be ferrimagnetic. SHENOY *et al.* (1969) found that orthopyroxenes are magnetically ordered when the ferrous ion concentration exceeds approximately 75 per cent. For more magnesium-rich compositions paramagnetic relaxation effects were observed at temperatures of 1·7°K. The magnetic properties of augite are unknown. FERNÁNDEZ-MORÁN *et al.* (1970) speculated that the rather unusual magnetic ordering in the lunar pyroxene could be due to iron-iron clustering in the approximately 300 Å-wide single-crystal bands depicted in the electron micrographs. This would imply a substantial enrichment of the bands in iron compared to the interband regions. This interpretation is inconsistent with the unmixing tie-lines in the pyroxene quadrilateral (e.g. YODER *et al.*, 1963). A similar but yet less drastic inconsistency was reported by BAILEY *et al.* (1970). However, in view of the difficulty of establishing the intrinsic chemical

compositions of single-crystal domains no definite conclusions can be made at this time.

These results, which are being further analyzed, illustrate the potential contribution of correlated electron optical and crystallographic studies to a better understanding of the intrinsic atomic organization of pyroxenes and their possible bearing on the crystallization and cooling history of the lunar igneous rocks.

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We wish to thank Professor HANS RAMBERG of the University of Uppsala for kindly providing us with XYZ orthopyroxene.

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CELL FINE STRUCTURE AND FUNCTION — PAST AND PRESENT

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SUMMARY

During the past 20 years, our research program has included the following related problems of nerve membrane ultrastructure which are particularly suitable for correlated electron microscopic investigations:

1. elucidation of the organization of cell membranes and of associated multi-enzyme and macromolecular components which carry out energy and information transduction functions, and

2. investigation of the association of nucleic acids and the protein synthetic machinery with cell membranes to gain a better understanding of membrane biosynthesis, including: (*a*) study of DNA and RNA conformations associated with membranes in chloroplasts, mitochondria and nerve cells; and (*b*) study of RNA polymerase and its participation in the differential RNA transcription upon DNA templates.

High resolution electron microscopy and electron optics have now progressed to a stage where they can contribute significantly to ultrastructural studies. Several new approaches in instrumentation, including the diamond knife [4] and the vacuum-tight microstage [5], have allowed us to examine biological specimens under conditions approaching their native hydrated state.

Using a specially-designed HU-200E high voltage microscope with improved point cathode sources [6], we have increased resolving and penetration power and reduced radiation damage (figs 1, 2). We have obtained resolutions of 2.06 Å in crystalline lattices and 4 Å point resolutions in 250 Å to 350 Å-thick biological specimens (figs 3–5). High resolution electron diffraction carried out with this microscope has yielded 50 to 100 diffractions for certain specimens as compared with 5 to 10 diffractions obtained with typical low voltage microscopes (fig. 6).

The development of the cryo-electron microscope operating with high-field superconducting solenoid lenses at liquid helium temperatures represents a significant instrumental advance. It provides superstable lenses; ultra-high vacuums; minimized specimen damage, contamination and thermal noise; and enhanced image contrast in a single system (fig. 7).

MEMBRANES

Elucidation of the molecular oganization of cell membranes is one of the fundamental problems of biomedical research and a major challenge to further progress in molecular biology.

Correlated ultrastructural and biochemical studies over the past few years have revealed certain general characteristics of membrane organization [7–10].

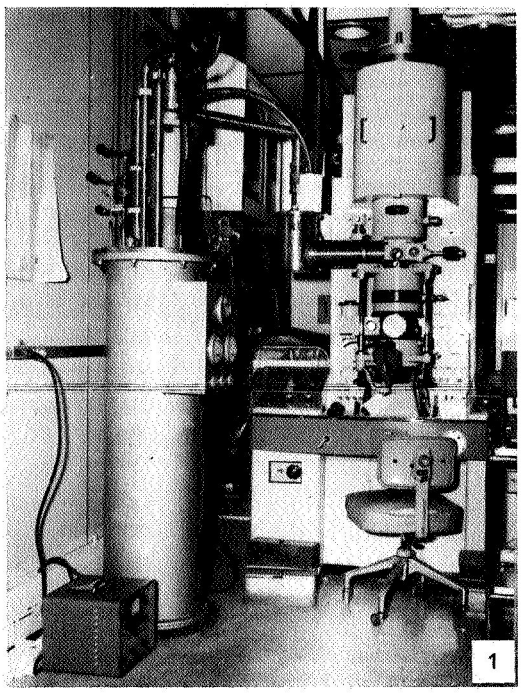

Fig. 1. High voltage 200 kV electron microscope with specially-designed helium cryostat specimen stage attached to closed-cycle superfluid liquid helium refrigerator with Collins heat exchanger and accessories for superconducting high voltage microscopy.

Coherent paucimolecular layers of indefinite lateral extension appear to consist of a periodic, hydrated lipoprotein substrate which is integrated with specific macromolecular repeating subunits organized in asymmetric paracrystalline arrays within the plane of the layers (figs 8, 9).

Work with David Green and his associates [11] has shown that membranes are made up by the stereospecific association of macromolecular repeating units of lipoprotein whose conformations are dependent on their association with the membrane substrate.

Further studies have indicated that many lipoprotein membranes, both native and artificial, respond in vivo as well as in vitro to the binding of specific ligands by some modification of their properties. This process reflects the rearrangement of membrane organization and, presumably, of the repeating unit's conformation (fig. 10).

Preliminary studies of thin (100 Å to 400 Å) sections of nerve myelin sheath and frog retinal rod outer segments have been made

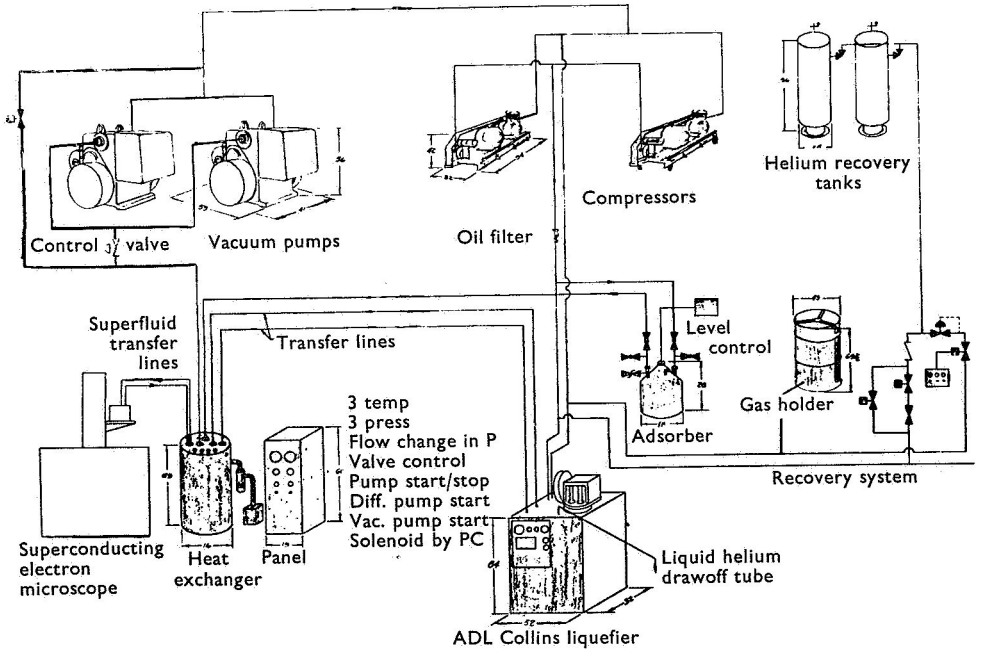

Fig. 2. Closed-cycle superfluid liquid helium refrigerator for superconducting high voltage cryo-electron microscope.

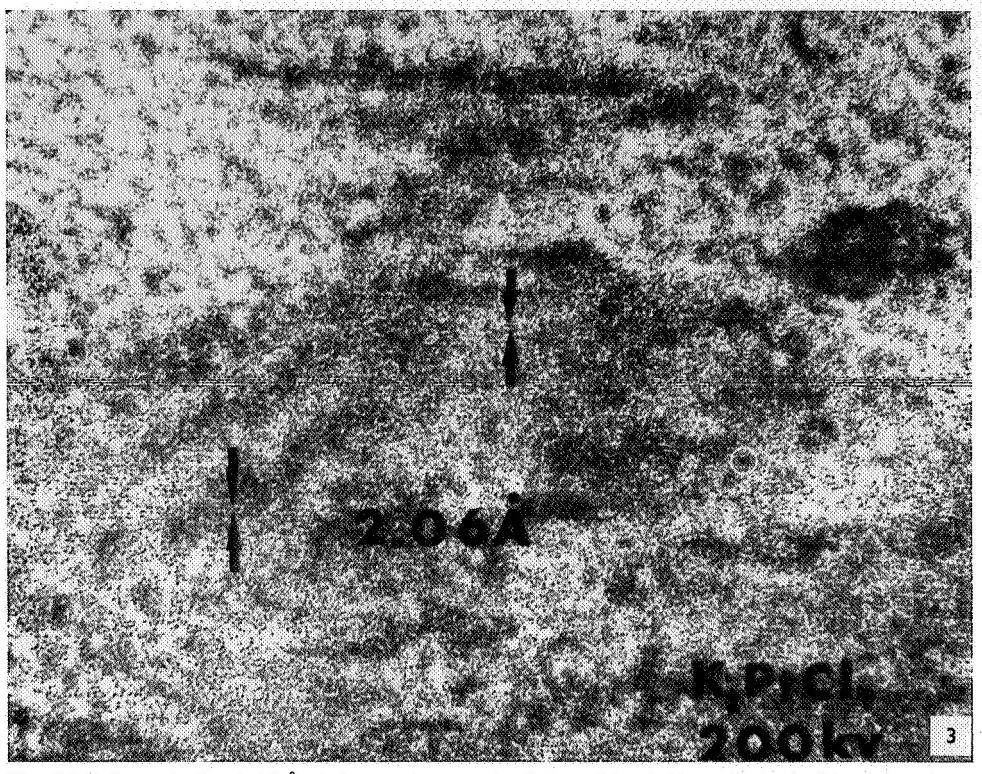

Fig. 3. High resolution 2.06 Å electron micrograph of crystalline lattice recorded with high voltage HU-200E microscope.

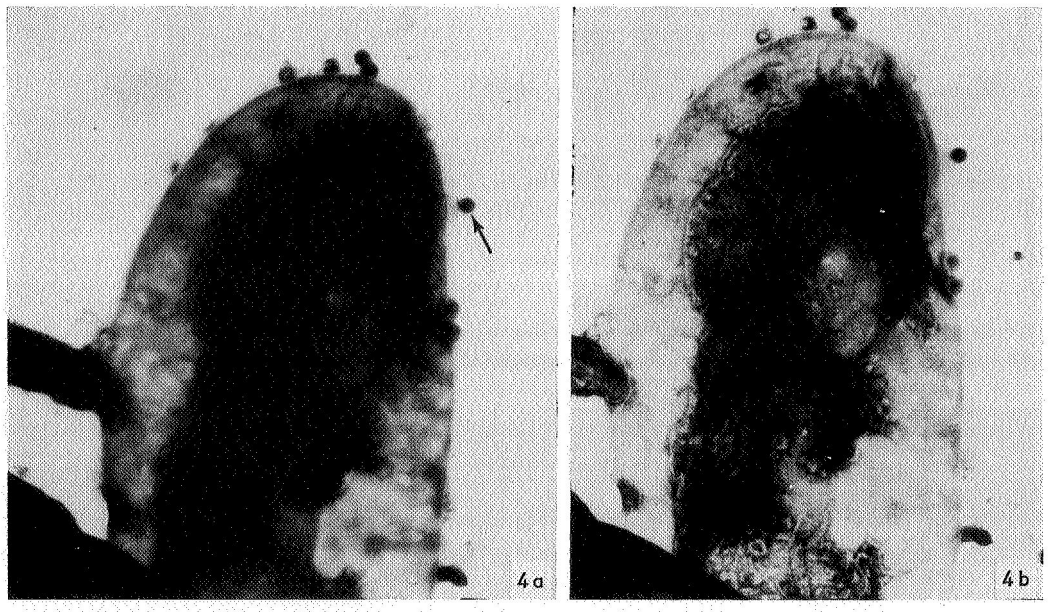

Fig. 4. (*a*) Electron micrograph of Phycovirus SMI A infecting blue-green algae recorded at 50 kV; (*b*) high voltage electron micrograph of Phycovirus SMI A infecting blue-green algae showing enhanced resolution and penetration (200 kV).

Fig. 5. High resolution 4 Å to 10 Å electron micrograph of thick 500 Å catalase crystal with high voltage HU-200E microscope.

using improved high resolution low-angle diffraction techniques. The diffraction patterns from selected membrane areas show reflections corresponding to periods of ca 180 Å in the radial direction and ca 60 Å to 160 Å in the plane of the membrane layers [7, 10, 11, 12] (fig. 11).

THE ROLE OF WATER

A major aspect of our biological investigations has been the concept of organized water as an integral structural component of biological systems, particularly of membranes.

We must assume that ordered water becomes specifically integrated in the highly organized three-dimensional macromolecular structures of the living systems. The abundance of postulated bulky species of water offers numerous possibilities ranging from the crystalline hydrate structures to other frameworks of approximately tetrahedral fourfold coordination [7].

Based on our earlier correlated studies of water using non-destructive methods such as nuclear magnetic resonance [13–15] and X-ray diffraction techniques [14, 16], the concept of a three-dimensional hydrated lipoprotein system was developed. This system provides a general structural framework for

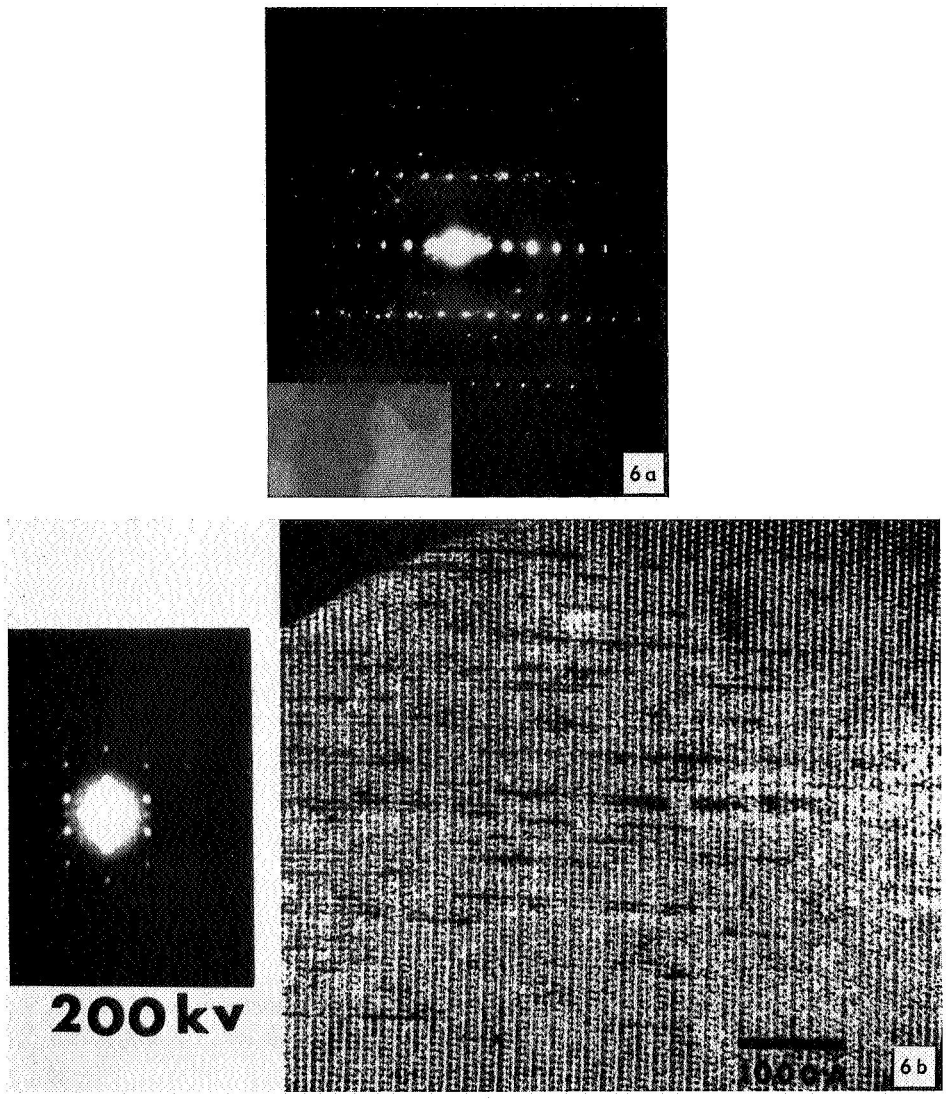

Fig. 6. (*a*) Calibration high resolution electron micrograph and electron diffraction of crystalline lattice; (*b*) high resolution 4 Å to 10 Å electron micrograph of thick 500 Å catalase crystal recorded with high voltage HU-200E microscope.

specialized macromolecular repeating units within the membrane layers [14, 16, 17, 18].

Although the main functional differences between membranes would depend upon the types of transducing units present and the complementary stereospecific configuration of the underlying substrate, this hydrated lipoprotein matrix could introduce a common unifying factor.

The water, particularly in close association with the ordered lipoprotein membrane systems, must likewise be highly ordered resembling "ice-like" hydration sheaths or "crystalline hydrate" lattices (fig 12).

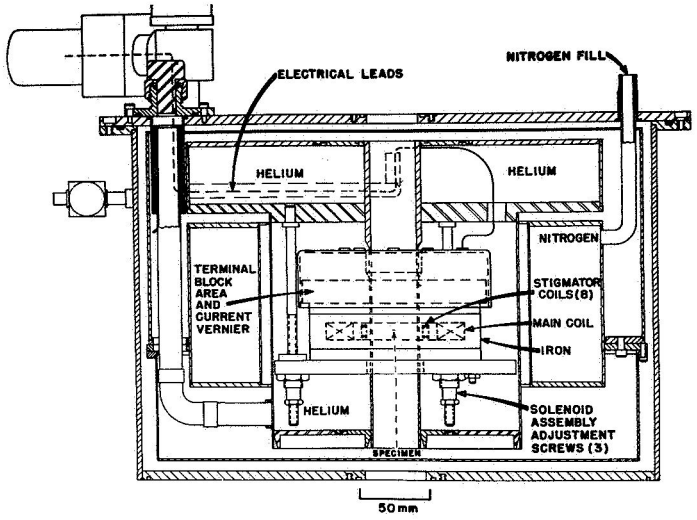

Fig. 7. Sketch of superconducting objective lens with stigmators and vernier coils of special design in liquid helium cold stage assembly for cryo-electron microscope.

These ideas have now been extended and experimentally verified by numerous investigators including Schultz and his associates. They have reported that our structural parameters have led to the formulation of a new model for the cellular plasma membrane [19, 20] (fig. 13).

They have been able to characterize ordered water in cellulose acetate and porous glass deslaination membranes. Above a certain diameter, they have found that each membrane pore is linked with a hydration sheath (ca 22 Å-thick) of highly hydrogen-bonded water in which salt is essentially insoluble. Ordered water almost entirely fills a pore with an ideal critical diameter of 44 Å.

In a later paper, they have expanded a concept first postulated by us that the development of the selective permeability of nerve membranes might be envisaged in terms of

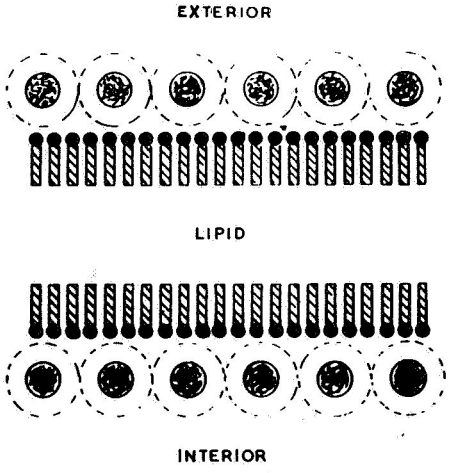

Fig. 8. "Paucimolecular" diagram of cell surface (Davson & Danielli).

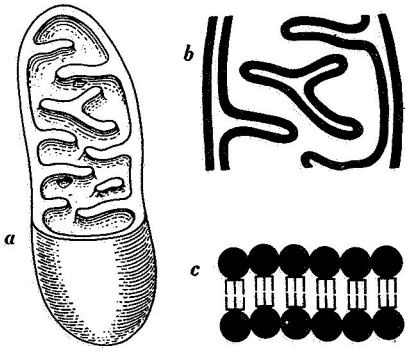

Fig. 9. Mitochondrial structure is basically that of a fluid-fluid vessel with an involuted wall (*a*). Closer analysis shows that the wall consists of a double membrane (*b*). Each membrane approximates the thickness of a single layer of protein molecules (spheres in *c*).

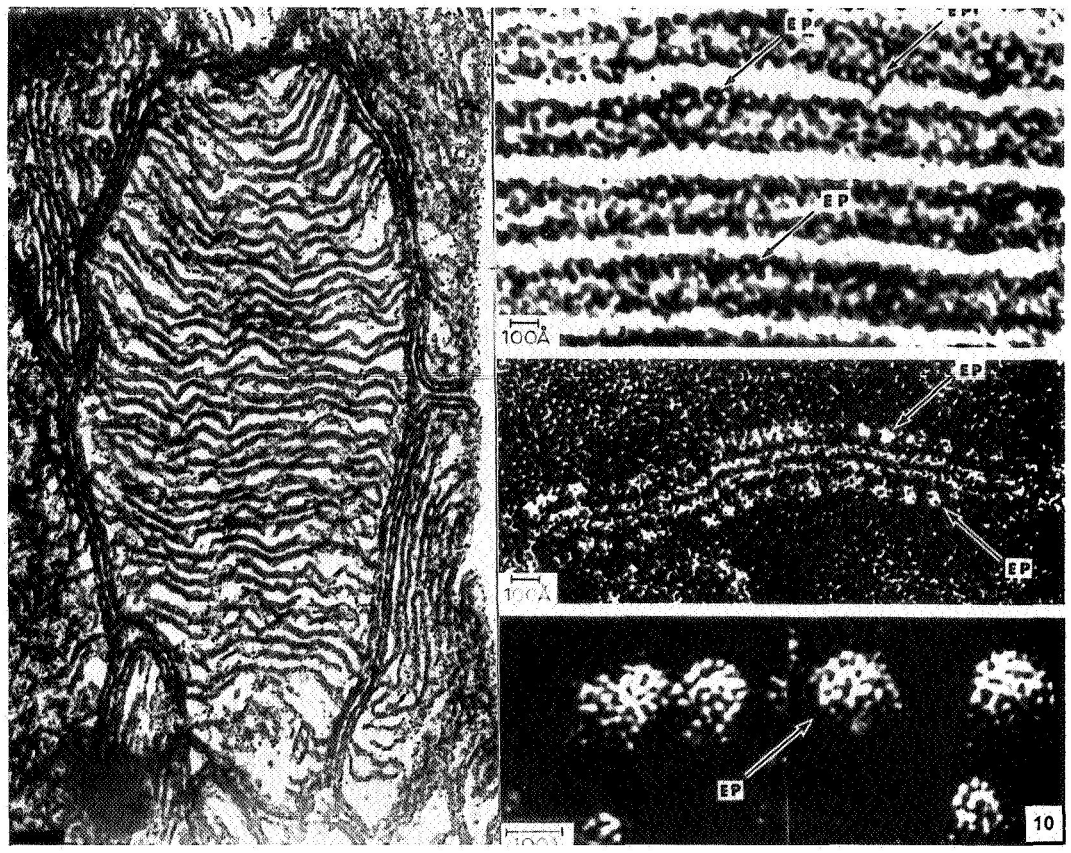

Fig. 10. Electron micrographs showing mitochondrial cristae and elementary particle (*EP*), i.e. repeating macromolecular subunit.

molecular "pores" lined with highly ordered water.

Lippincott and his associates [21] have recently reported that the infrared and Raman spectra of a form of water prepared in fused quartz capillaries and previously designated as anomalous water have been obtained. According to their interpretation of this data, new and previously unreported strong symmetric O–H–O bonds are formed. These bonds are regarded as responsible for the remarkable properties of the material and have considerable covalent character. They are so strong that they cannot be considered as normal O···H hydrogen bonds. They have concluded that the material is a true polymer of water, and, therefore, they have called it "polywater".

DNA AND RNA

In earlier experiments with Dr Christopher Woodcock [22], we successfully applied techniques for the isolation and purification of spinach chloroplasts on a micro-scale (fig. 14). Following osmotic shock, we were able to visualize the DNA associated with each chloroplast by electron microscopy.

DNA molecules extracted from purified chloroplasts were also analyzed. Under con-

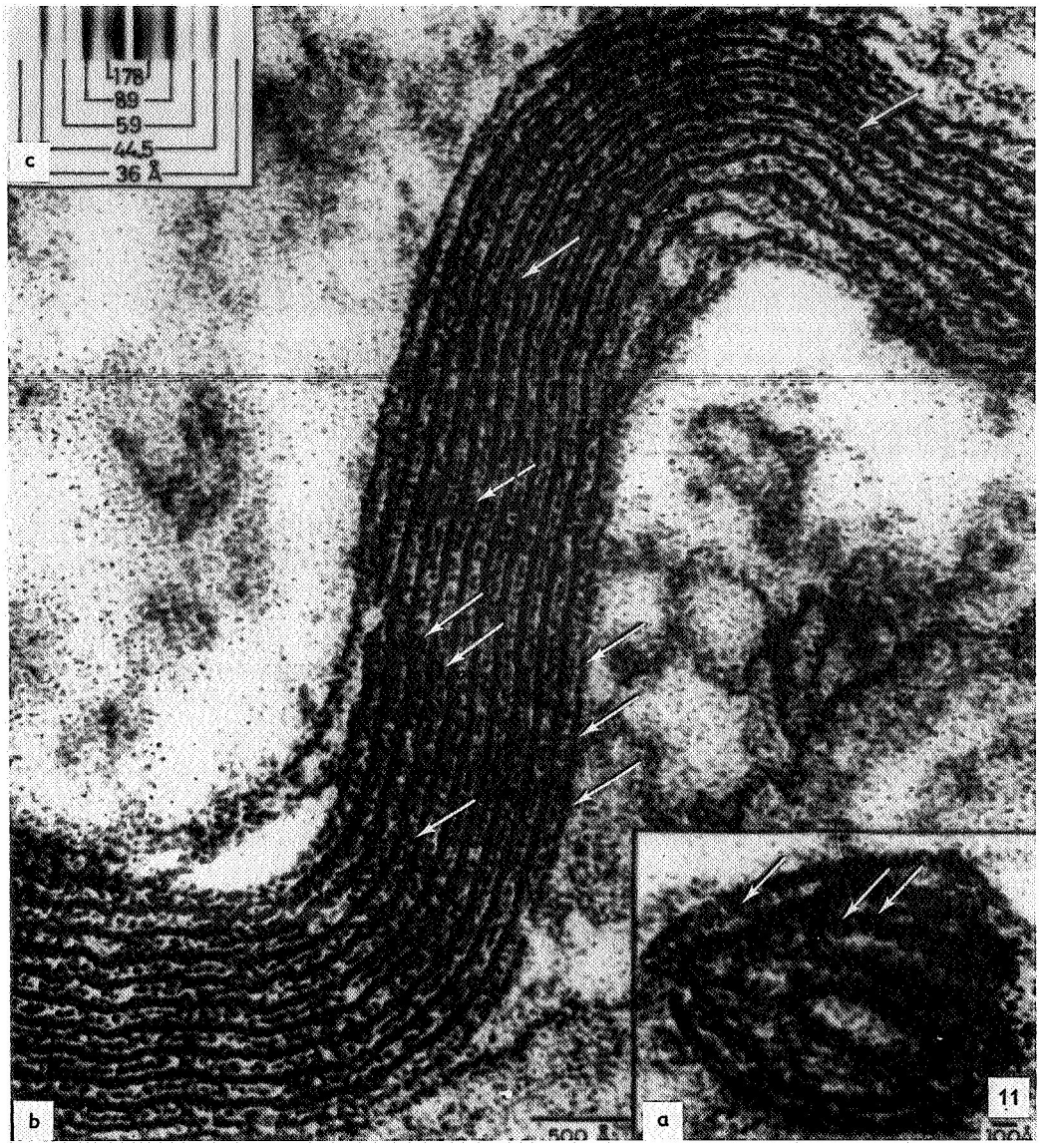

Fig. 11. (*a*) High resolution electron micrograph of myelin sheath segment from transverse thin section of frog sciatic nerve showing concentric array of dense and intermediate layers. Particulate subunit structures (*arrows*) are regularly found within the plane of the layers in these well-preserved, osmium-fixed, low-temperature preparations; (*b*) axonal mitochondria from a similar preparation demonstrating globular subunits in the dense layers of the cristae; (*c*) low-angle X-ray diffraction pattern of fresh sciatic nerve featuring a fundamental period of 178 Å with typical alternation of the intensities of the even and odd orders.

trolled conditions, we have consistently observed two major DNA conformations and a characteristic association with the chloroplast membrane system (fig. 15).

At the present time, DNA is visualized as being intimately associated in specific regions with the membrane system. A highly organized spatial orientation can be anticipated,

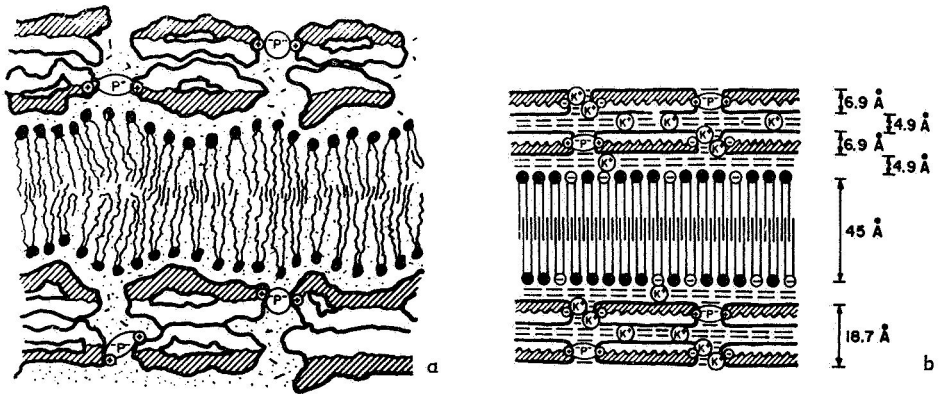

Fig. 12. (*a*) Diagram of a resting membrane illustrating the unit membrane concept; (*b*) schematic representation of the depolarized membrane (O. Hecheter).

assuming that the DNA and the self-duplicating mechanism of the chloroplast must conform to the paracrystalline arrangement of the membranes. Moreover, as the chloroplast is a self-propagating, multicomponent structure, the genome which ensures its form and continuity may have commensurate complexity which we are only now beginning to discover.

Discovery of the characteristic nucleic acids in mitochondria and the demonstration of a protein biosynthetic system have recently confirmed and extended earlier work to provide significant support for the semi-independence or autonomy of these membranous organelles.

Attachment of membrane pieces to DNA and the observed association of mitochondrial DNA with cristae may possibly represent sites where replication is initiated.

Accumulating evidence indicates that in addition to DNA, RNA, ribosome-like particles and RNA polymerase-like systems are found in mitochondria from different sources. This new information furnishes the basis for a working hypothesis implying that mito-

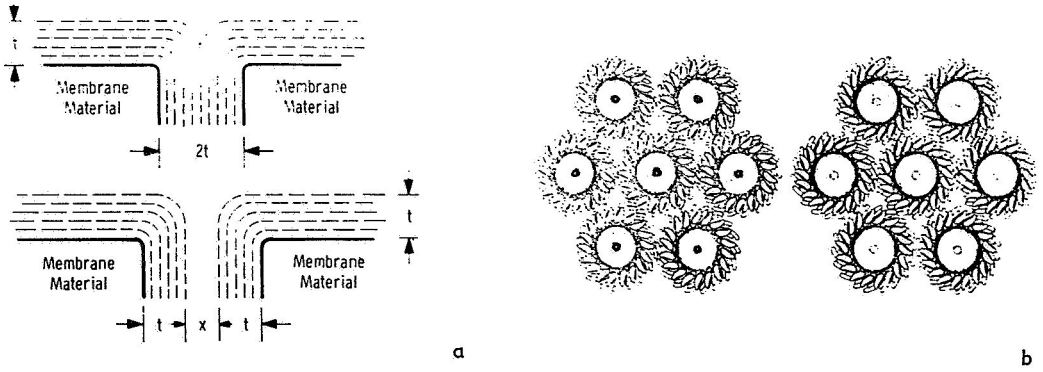

Fig. 13. (*a*) Diagrammatic representation of ordered water sheath (thickness *t*) in the vicinity of a pore in a hydrophilic membrane. Top diagram shows critical diameter (*2t*) of hole filled with ordered water that will exclude all ions; bottom diagram shows hole lined with ordered water that will allow ions of width ($< \times$) to pass through unordered water channel of diameter ($\times$); (*b*) paste-up approximation of close packing of lipid rings of hexagonal subunits in resting configuration (*left*) and in open configuration (*right*) (Schultz et al.).

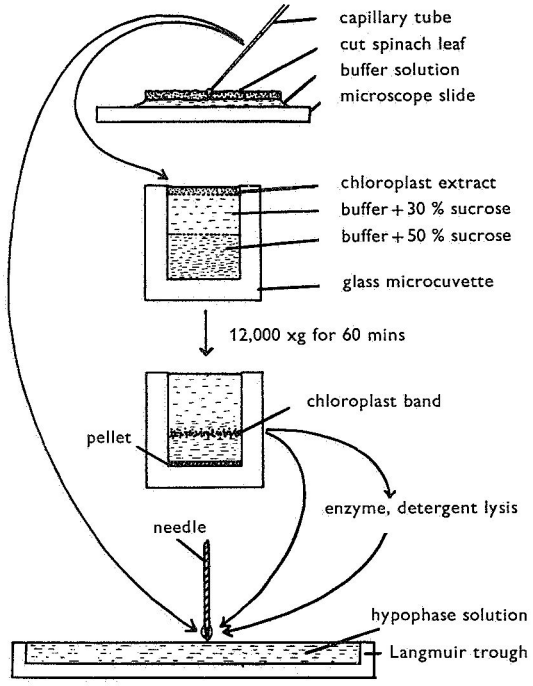

Fig. 14. Scheme for the extraction, purification and spreading of chloroplasts and chloroplast DNA.

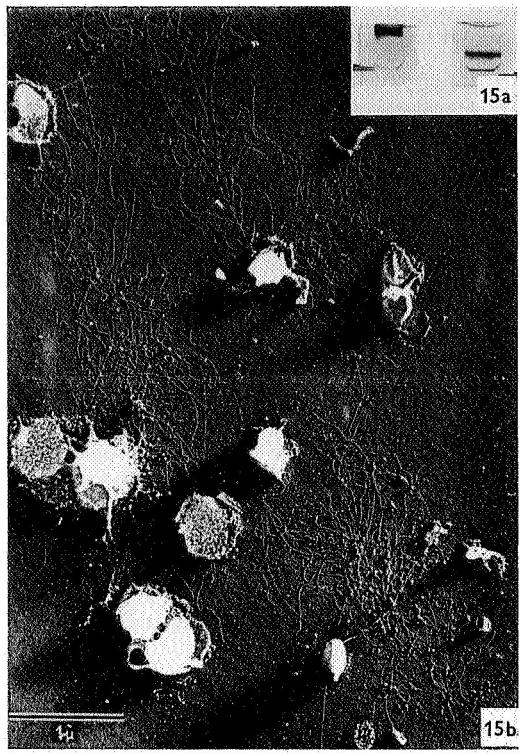

Fig. 15. (*a*) Microcuvettes before and after centrifugation; (*b*) portion of an osmotically disrupted chloroplast showing DNA strands associated with membranes. Platinum shadowed.

chondria (and possibly chloroplasts) possess their own genetic information and the necessary mechanism to express it in an autonomous synthesis of proteins.

The enzyme RNA polymerase plays a key role in the transfer of genetic information through its participation in the differential RNA transcription upon DNA templates. Confirming the results of earlier workers, we have studied the structure and physical properties of RNA polymerase molecules from *E. coli* [23].

In order to obtain more information on the manner in which RNA polymerase initiates transcription of RNA upon DNA templates, we are carrying out correlated electron microscopic studies on the binding of RNA polymerase to different types of DNA. The attachment to circular forms of DNA (e.g. from φX 174) is of particular interest, and we are studying it together with Richard Gumport and Samuel Weiss (figs 16, 17).

These types of studies are all built on the concepts of cell organization first adumbrated by Caspersson and his associates in the early 1940's. The improved instrumentation and techniques for electron microscopy which are continually being developed have permitted us to get a closer glimpse of our molecular organization. Perhaps in the near future we will be able to do more than observe these critical life-chains. In successfully manipulating and altering them to rid mankind of its hereditary ailments, we will be fulfilling a basic goal of all biomedical research [24].

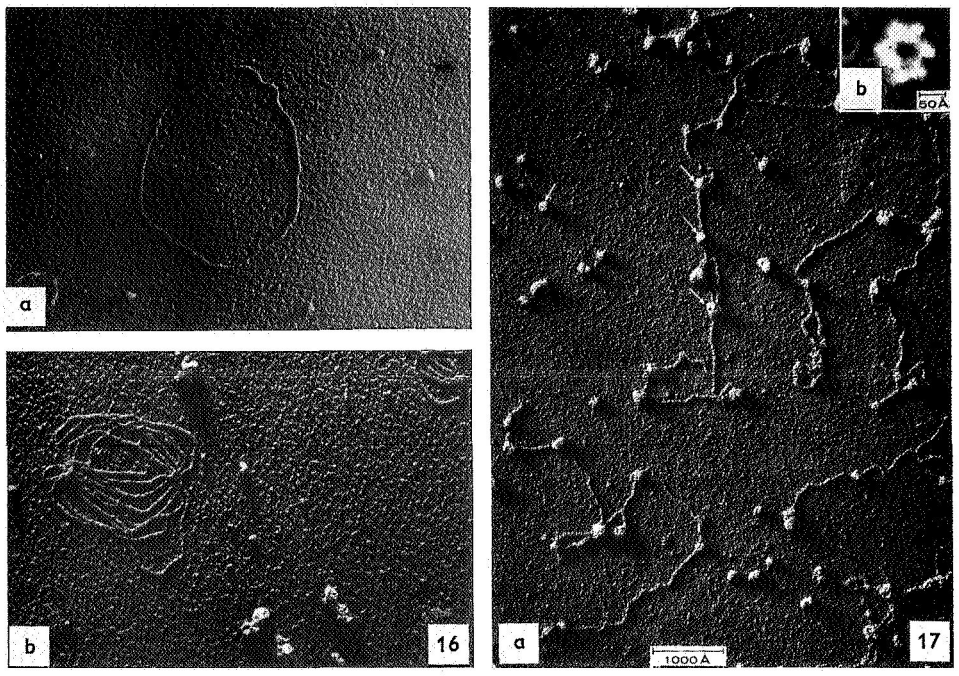

Fig. 16. Electron micrographs of Kleinschmidt preparations showing: (*a*) Circular DNA of $\varphi \times 174$rf 21S; (*b*) molecular complexes resulting from the reaction of this DNA with *E. coli* RNA polymerase upon addition of the four regular nucleotide triphosphates: ATP, CTP, GTP, UTP. After 15 min at room temperature characteristic convolutes formed by filaments of varying widths are found in close association with DNA-enzyme complex.

Fig. 17. Electron micrographs showing: (*a*) attachment of RNA polymerase molecules (*arrows*) to DNA strands as seen in shadowed preparations; (*b*) DNA-dependent RNA polymerase molecules from *E. coli* prepared by the Chamberlin & Berg procedure appear to consist in negatively stained preparations of six subunits arranged in a hexagon with a cross-section of 120 Å to 130 Å. These correlated electron microscopic and biochemical studies are expected to yield further information on RNA polymerase and its participation in the differential RNA transcription upon DNA templates which is of fundamental importance in the regulation of protein synthesis and function in nerve cell membranes and their derivatives.

I wish to thank M. Ohtsuki for technical assistance in the electron microscopy, C. L. Hough, C. Weber and G. Bowie for photographic reproduction; V. Iglesias, M. Hanaoka, A. Hibino, R. Vicario, H. Krebs and G. Arcuri for specimen preparation; S. Rowe and J. Richardson for editorial assistance, and S. Erikson and C. Benitez for administrative assistance.

It is a pleasure to thank Mrs Dagmar Nelson for all the help she gave me with unfailing grace during the memorable years which I spent at the Institute for Cell Research and Genetics.

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HIGH RESOLUTION ELECTRON MICROSCOPY OF CELL MEMBRANES AND DERIVATIVES

(A paper to be presented at the 7th International Congress on Electron Microscopy, Grenoble, France, August 30 to September 5, 1970)

H. Fernandez-Moran, M. Ohtsuki and C. Hough
Department of Biophysics, University of Chicago, Chicago, Illinois U.S.A.

The research and development program carried out in our special facility for electron microscopy reflects the prevalent trend of inter-disciplinary cooperation, since it not only focuses on biological systems but also encompasses related fields and even extends to studies of extraterrestrial specimens. Deriving support from the synergetic effects of new concepts and technologies, its major objectives comprise: 1) Improvement and practical application of instrumentation and preparation techniques for high resolution, high voltage and low temperature electron microscopy and diffraction, expecially directed towards correlative studies of cell membranes and associated multi-enzyme complexes invested with energy and information transduction functions. A major role is assigned to ordered water specifically integrated in the highly organized three-dimensional macromolecular structure of all biological systems. Examination of biological specimens under conditions approaching their native hydrated state is therefore considered to be the prime requirement despite severe experimental difficulties. The following approaches appear to be the most promising: a) High voltage electron microscopy increases penetration power, reduces specimen radiation damage and chromatic aberration. By working in the range of 200 kV, resolutions of 2.06Å (Fig. 2) have been consistently obtained in relatively thick periodic specimens, and point resolutions of 5 to 10Å in 300Å to 500Å biological specimens (Figs. 3,4). It is now possible to examine whole mounts of bacteria, algae, mitochondria, etc. which were hitherto impenetrable. Ivenstigation of thick sections of lunar pyroxene prepared by cleavage and diamond knife ultramicrotomy (Fig. 3b) illustrates the potentialities of this technique. Specimens enclosed in vacuum-tight microchambers with multiple cavities of 100Å to 1000Å prepared by precision micro-engraving techniques can be examined "wet" with microbeam illumination at room temperature or "supercooled" at low temperatures, extending our earlier work. Observation of hydrate unstained specimens will require high resolution phase contrast imaging with aligned condensor and objective zone-plate apertures provided with electrical and magnetic fields to control phase shift, astigmatism and aberration correction. b) Combination of electron microscopy with small angle electron diffraction using improved point cathode sources is valuable in the study of catalase and multi-enzyme complexes (Fig. 1,3) confirming and extending work by R.P. Ferrier. c) Computer enhancement of periodic images has proved rewarding after R. Nathan clearly demonstrated that an extreme improvement can be obtained in the signal to noise ratio by translating the image by the amount of the periodicity and superimposing the image upon itself. As shown in Fig. 1b, computer enhancement of our original catalase micrograph brings out further detail and displays images where intensities are contoured.

2) Further development of the cryo-electron microscope at liquid helium temperatures with superconducting lenses and preferably operating at high voltage represents probably the most significant approach, since it provides optimized electron-optical conditions with minimized specimen damage and enhanced image quality in a single system. Ultraminiaturized integrated circuits which could serve as submicroscopic prosthetic sensors can also be produced by related techniques. We may well be on the threshold of a new era enabling us to conduct electron optical studies under conditions of minimum perturbation while establishing a parallel feedback link through homologous duplication of the microcomponentry of living systems. We wish to thank H. Krebs, R. Vicario, G. Bowie, C. Weber, G. Arcuri, S. Rowe, J. Richardson for their valuable assistance. Supported by Pritzker Fund, L. Block Fund of University of Chicago, NASA NGL 14-001-012 and NIH GM 13243-05.

HIGH VOLTAGE ELECTRON MICROSCOPY AT LIQUID HELIUM TEMPERATURES

(A paper to be presented at the 7th International Congress on Electron Microscopy, Grenoble, France, August 30 to September 5, 1970)

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Advances in High voltage electron microscopy and low temperature physics enable us to continue collaborative research programs designed to achieve enhanced resolution and controlled manipulation of molecular structure under conditions of reduced entropy emphasizing: 1) Development and application of improved high-voltage cryo-electron microscopes with superconducting lenses operating in conjunction with a specially-designed Collins closed-cycle superfluid helium refrigerator. (Fig. 1) After critical testing, the centrally-located unit with its novel heat exchanger and long transfer lines demonstrated for the first time the feasibility of supplying liquid and superfluid helium at 1.9°K with a 20-watt refrigeration capacity to microscope cryostats at a rate of 5 to 8 liters per hour. During more than a year of flawless performance and unprecedented operational economy and reliability, the system has consistently produced superfluid helium with its exceptional thermal conductivity and non-viscous flow properties. The large capacity, unique heat transfer and quantized rotational properties of the "superfluid" helium system enable it to supply both lens cryostats and compact superconducting linear accelerators (based on one built by Fairbanks at Stanford with 6MeV electron beam stabilized to better than one part per million) to provide high voltage electron sources. Such "integrated cryo-electron microscopes" would exhibit unmatched stability of lens excitation current and high voltage (ca. 5 kV to 10 MeV), correction of spherical and chromatic lens aberrations including trapped-flux, phase zone apertures and coherent electron point cathodes operating in cryogenic ultrahigh vacuums to decisively reduce radiation damage, contamination and thermal noise while enhancing image quality with an optimized image intensifier operating at liquid helium temperatures. Compared with the unusual size and costs of future high voltage instruments, this new generation of multi-purpose cryo-electron microscopes would be preferable, especially now that working expenses and operating ease of the closed-cycle superfluid unit (able to supply several microscopes) have eliminated the last practical hindrance.

2) Improved liquid helium cold stage assemblies (Fig. 2) extend the temperature range from about 1°K to 0.06°K using cryostats with $^3He/^4He$ dilution refrigerators. Even lower temperatures in the microdegree range could be attained by adiabatic demagnetization of nuclear spins using high field superconducting magnets of objective lenses as dual imaging components and high magnetic field sources coupled with cryostats containing paramagnetic specimen holders. This logical extension of inherent properties of such a cryo-microscope may permit us to apply techniques of direct electron-optical observation to visualization of unexplored domains of basic phenomena related to properties of matter subjected to the ultimate "entropy squeezer," allowing cryo-electron optics to become the most refined direct probe into the realm of vanishing entropy for the physicist and the biophysicist who has yet to fathom living matter confined to the boundaries of the quantum state. Fig. 3 illustrates the anomalous electron transparency of thick lead films which is even more marked at 200 kV than at 40 kV as first described by Boersch. Fig. 4 shows image quality of catalase and asbestos even after prolonged exposure at 4.2°K. Examples of ultraminiaturized electronic components prepared at 1.8°K and applications of associated trapped-flux patterns as computer memory elements will also be presented. I wish to thank Prof. S. C. Collins, M. Streeter, R. Osburn, T. Helpern, H. Krebs, M. Ohtsuki, C. Hough, R. Vicario, G. Bowie, C. Weber, and R. Szara for their valuable assistance. Supported by Pritzker Fund, L. Block Fund of University of Chicago, NASA NGL 14-001-012 and NIH GM 13243-05.

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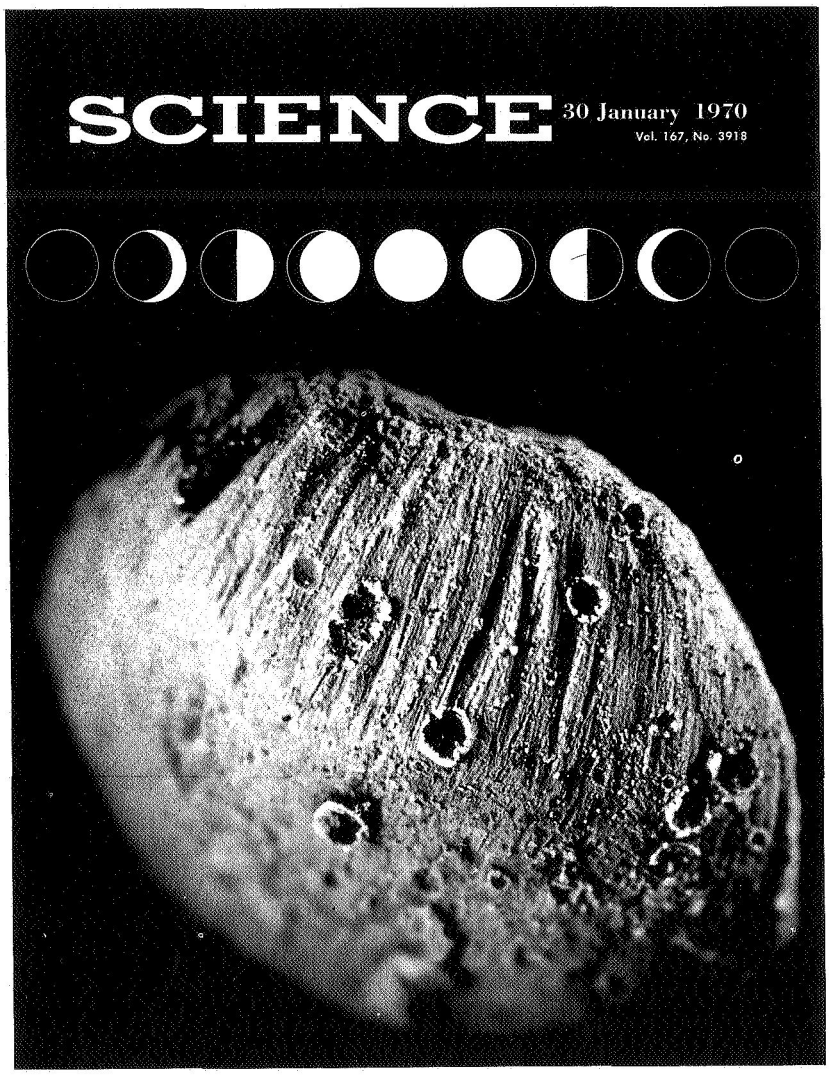

Mossbauer Effect and High-Voltage Electron Microscopy of Pyroxenes in Type B Samples

H. Fernandéz-Morán, Stefan S. Hafner, Mitsuo Ohtsuki and David Virgo

Mössbauer Effect and High-Voltage Electron Microscopy of Pyroxenes in Type B Samples

Abstract. *Site occupancy numbers for ferrous iron, magnesium, and calcium at the M1 and M2 sites in lunar clinopyroxenes are estimated from nuclear gamma-ray resonant absorption spectra of ^{57}Fe. The cation distribution is ordered; calcium and magnesium prefer M2 and M1, respectively. The distribution corresponds to an equilibrium at a temperature lower than 680°C. Crystals cleaved and sectioned by diamond-knife ultramicrotomy were examined by high-voltage (200 kv) electron microscopy and diffraction. Uniform 300- to 600-Å-wide bands that correspond to single crystal domains were found. Correlation of the bands with magnetic ordering at low temperatures is considered.*

The crystallization and subsequent cooling history of pyroxenes is reflected in their exsolution phenomenon and in the cation distribution over structural sites. Therefore, studies of the domain structure in pyroxene crystals and of the intrinsic site occupancy in the distinct phases are important (*1*).

Clinopyroxenes separated from the type B specimens 10003 and 10044 were crushed to a grain size of approximately 50 μm and further separated into fractions of different Mg,Fe,Ca compositions by means of heavy liquids. Each fraction yields a distinct resonant absorption spectrum (Fig. 1). The nuclear quadrupole doublets due to Fe^{2+} at the M1 and M2 sites are generally well resolved. The spectra of two fractions from 10044 are shown in Fig. 1. Isomer shifts and nuclear quadrupole splittings (peak to peak separation) of the clinopyroxene from rock 10044 and those of a terrestrial augite with similar chemical composition and an iron-rich orthopyroxene are given in Table 1. The widths at half peak height are approximately 0.36 mm/sec.

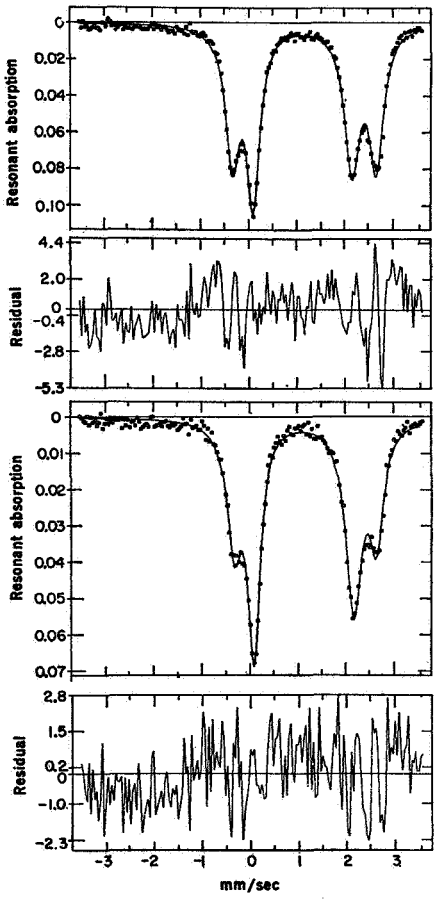

Fig. 1. Resonant absorption spectra of ^{57}Fe in clinopyroxene from specimen 10044. Upper spectrum: iron-rich fraction 10044-P3. Lower spectrum: magnesium-rich fraction 10044-P2. The solid line is a least squares fit (13 variables) to the uncorrected data. Absorbers were held at 77°K. Outer peaks: Fe^{2+} at M1; inner peaks: Fe^{2+} at M2.

The x-ray diffraction powder data indicate that the 10044 pyroxene consists almost exclusively of augite, whereas some fractions from 10003 also include pigeonite. However, measurements of isomer shifts and quadrupole splittings at 77°K in terrestrial pyroxenes with compositions within the enstatite-diopside-hedenbergite-ferrosilite quadrilateral show that the shifts and splittings are only slightly affected by small changes in Mg,Fe,Ca composition or by changes in crystal symmetry, for instance from space group $C2/c$ to $P2_1/c$. The data of Table 1 are consistent with those observations. Therefore, the resolution of the M1 and M2 doublets, for instance in the case of separates from rock 10003, is not surprising, and the hyperfine data of ^{57}Fe can be interpreted in terms of average occupancy numbers.

Average compositions and site occupancy numbers of the two chemically distinct 10044 fractions are shown in Table 2. The Mg,Fe,Ca distribution is principally an ordered one, M2 being almost exclusively occupied by Ca and Fe^{2+}, M1 being occupied by Mg and excess Fe^{2+} (Table 2). No significant Fe^{3+} peaks could be detected.

Estimates of the stability field of the observed cation distribution can be made from heating experiments. Speci-

mens of clinopyroxene 10044-P2 were heated at 675°C for 76 hours and at 1000°C for 17 hours. A significant change in the relative doublet intensities was observed (Table 2). Therefore, the cation distribution in the natural 10044 clinopyroxene corresponds to an equilibrium temperature lower than 675°C.

Studies of the cation distribution in rapidly cooled volcanic orthopyroxenes (*2*) and kinetic studies of the cation exchange process (*3*) suggest that partial ordering of cations in lunar clinopyroxenes may proceed rapidly during initial quenching from a high temperature but complete order is only attained after significantly long geological times at low temperatures. Disordered cation distributions are attained by initial rapid cooling. For comparison some data on the terrestrial Kakanui augite (*4*) are given in Table 2. The site occupancy for this volcanic sample is considerably complicated by the presence of other cations (*5*) but the significantly higher relative proportions of Mg in the M2 sites is consistent with a more rapid cooling history in comparison with the augite from rock 10044. The change of site occupancy in lunar augite is comparable to the change in ordered orthopyroxenes heated at the same temperature. The slightly smaller change in the lunar specimen is indicative of a somewhat larger Gibbs free energy difference for the Mg,Fe^{2+} exchange reaction between M1 and M2 at 1000°C.

Table 1. Nuclear quadrupole splittings and isomer shifts of Fe^{2+} in lunar and terrestrial pyroxenes at 77°K.

Sample	Quadrupole splitting (mm/sec)		Isomer shift referred to metallic iron (mm/sec)	
	M1	M2	M1	M2
10044-P2	2.92	2.06	1.29	1.26
10044-P3	2.96	2.03	1.29	1.26
10044-P2 heated 675°C	2.91	2.04	1.28	1.26
10044-P2 heated 1000°C	2.92	2.05	1.28	1.26
Kakanui-Augite	2.80	2.09	1.26	1.25
Orthopyroxene XYZ	3.10	2.04	1.29	1.26

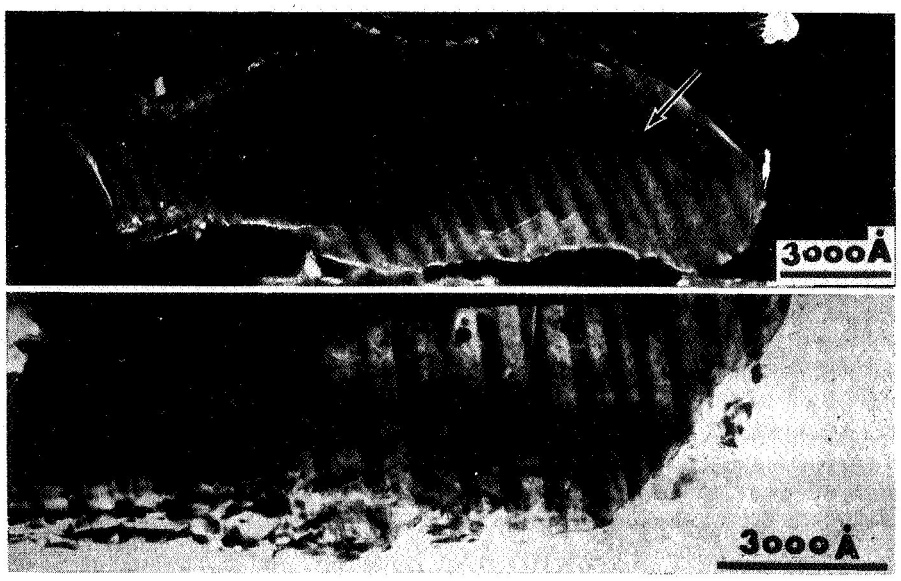

Fig. 2. High-voltage, dark field electron micrograph of cleaved clinopyroxene 10044 (above) and high-voltage electron micrograph of iron-rich clinopyroxene 10044-P3 showing uniform dense bands which are parallel (001) and irregular granules (below).

Pyroxenes cleaved and sectioned by diamond knife ultramicrotomy (*6*) and mounted directly on thin film specimen grids were examined by high voltage (200 kv) electron microscopy under conditions of increased penetration power and decreased specimen damage (*7*).

In crystals from fraction 10044-P3, regularly spaced, dense bands (Fig. 2, dark areas) with widths of 300 to 600 Å were recorded in approximately 2000 plates. These uniform bands appear to be single crystal domains and are oriented with their long axis in the plane of the crystalline layers, approximately normal to crystallographic *c*. Intrinsic lattice spacings of 2.5 Å (probably d_{002}) can be detected within the bands parallel to their long axis.

The bands resemble electron-optical images of magnetic domain walls as seen in thin layers of magnetic materials (*8*). They are predominantly seen in iron-rich (10044-P3) crystals but are absent in magnesium-rich (10044-P2) crystals and in the terrestrial orthopyroxene XYZ. In this connection resonant absorption spectra of specimen 10044-P3 taken at low temperatures do reveal magnetic ordering, below a Néel point of approximately 20 to 30°K. However, it is interesting to note that iron-bearing chain silicates are generally not mag-

Table 2. The Fe^{2+} distribution data over M1 and M2 sites in lunar and terrestrial pyroxenes. The Fe^{2+} distribution numbers were determined from the ^{57}Fe resonant absorption spectrums. The site occupancy was calculated from the distribution numbers assuming a preference of Ca for M2. Al, Ti, and Mn are ignored; suggested values are Al = 0.03, Ti = 0.03 and Mn = 0.02 (*10*). En, enstatite; Fs, ferrosilite; Wo; wollastonite.

Sample	Molecular composition	Fe^{2+} distribution numbers		Site occupancy					
				M1			M2		
		M1	M2	Mg	Fe	Ca	Mg	Fe	Ca
10044-P2	$En_{0.44}Fs_{0.20}Wo_{0.36}$	0.36	0.64	0.86	0.14	0	0.02	0.26	0.72
10044-P3	$En_{0.36}Fs_{0.34}Wo_{0.30}$	0.46	0.54	0.68	0.32	0	0.03	0.37	0.60
10044-P2 heated to 675°C		0.38	0.62	0.85	0.15	0	0.03	0.25	0.72
10044-P2 heated to 1000°C		0.40	0.60	0.84	0.16	0	0.04	0.24	0.72
Kakanui-augite*		0.34	0.66	0.72	0.06	0	0.19	0.12	0.62
Orthopyroxene XYZ	$En_{0.12}Fs_{0.85}Wo_{0.02}$	0.447	0.534	0.24	0.76	0	0.02	0.94	0.02

*0.90 Mg, 0.21 Fe, 0.61 Ca, 0.33 Al, 0.09 Na, 0.02 Ti per six oxygen atoms (*5*).

netically ordered, even at very low temperatures, especially if the amount of diamagnetic cations (magnesium, calcium) substituting for iron at the octahedrally coordinated positions is larger than 25 percent as in the 10044-P3 augite (*9*). We believe that the observed ordering is due to iron-iron clustering in the single crystal domain bands as revealed by electron microscopy (Fig. 2). In the domains between the bands, clustering of Mg,Ca seems likely. A statistical estimate shows that the total volume of the bands and interband domains within each crystal is about the same. Thus, a speculation on their respective chemical compositions can be made. If one assumes the extreme case that the ferrous ions are entirely located within the bands one is led to the pigeonite composition $En_{0.19}Fs_{0.68}Wo_{0.13}$ for the bands and an almost pure diopside of the composition $En_{0.53}Wo_{0.47}$ for the interband domains (molecular percent). The speculated band composition is consistent with the Fe^{2+} distribution data for 10044-P3 in Table 2. If one assumes complete ordering of Mg and Ca in the bands, the Fe^{2+} site occupancy in M1,M2 is 0.62, 0.73, respectively. This occupancy could certainly produce magnetic ordering at low temperature due to M1-oxygen-M2 superexchange.

The electron microscopic studies suggest an unexpected complexity in the intrinsic atomic organization of the clinopyroxenes from sample 10044. While these may indicate implications on the history of the crystals with respect to temperature and pressure, more detailed investigations will be needed for definite conclusions and their relevance.

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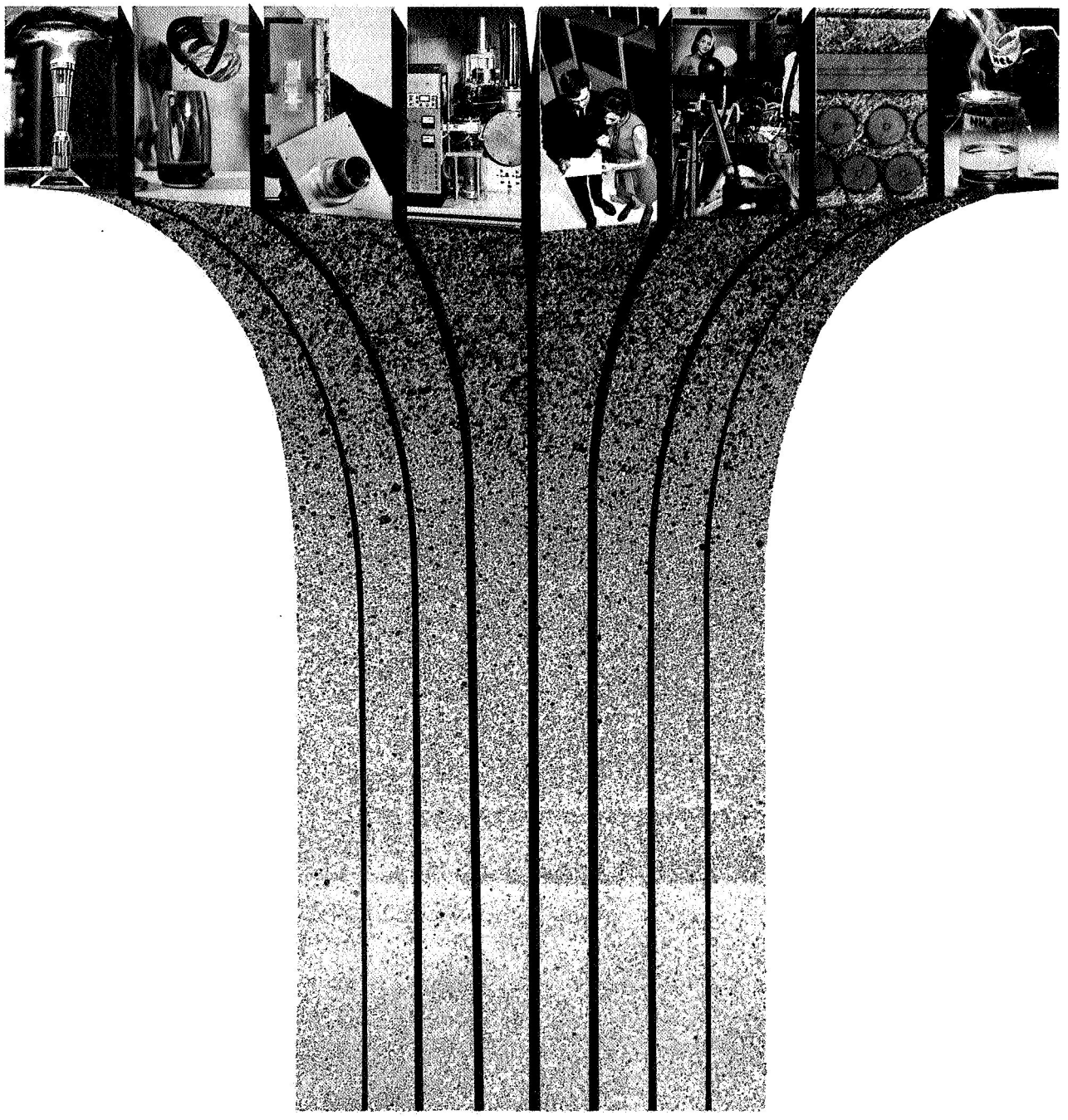
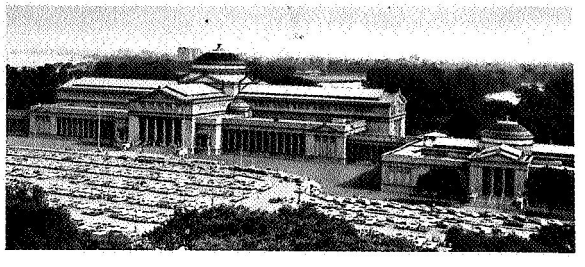
11. Mössbauer spectroscopy was aided by Mrs. L. Century, Miss B. Janik, and Mr. H. P. Weber and supported by NASA grant NAS-9-8080. Electron microscopy was aided by Mr. C. L. Hough, Mr. C. Weber, and Mr. G. Bowie for the photographic reproduction; Mrs. V. Iglesias, Misses A. Hibino and M. Hanaoka, Mr. R. Vicario, Mr. H. Krebs, and Mr. G. Arcuri for specimen preparation; Miss S. Rowe for editorial assistance; and Mrs. S. Erikson for administrative assistance. It was supported by the Pritzker Fund, the L. Block Fund, and the Otho Sprague Memorial Fund of the University of Chicago and NASA grant 14-001-012 and NIH grant GM-13243-05.

4 January 1970

Applying Emerging Technologies



Reprint from the Proceedings of the fifth annual
NATIONAL CONFERENCE ON INDUSTRIAL RESEARCH
September 18 and 19, 1969 at the Museum of Science and Industry in Chicago



Microminiaturization Panel

Data 'Reduction' for Information Retrieval

by Dr. Humberto Fernandez-Moran
Professor of Biophysics,
University of Chicago

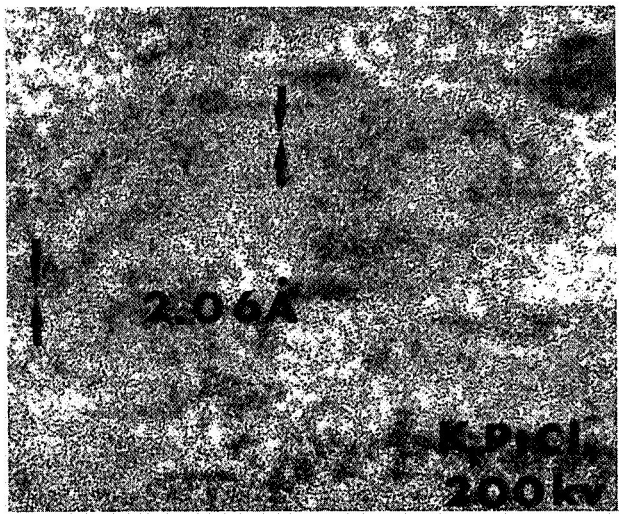
DATA 'REDUCTION' FOR INFORMATION RETRIEVAL

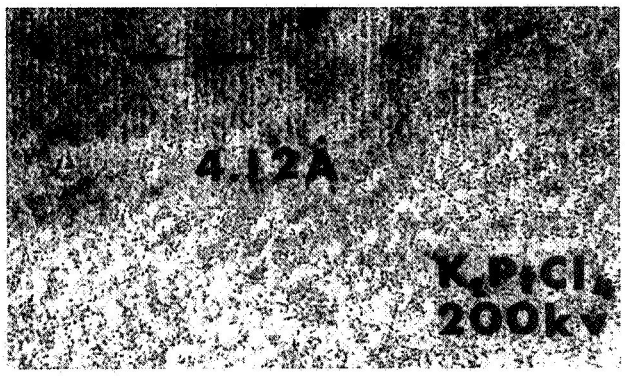
by Dr. Humberto Fernandez-Moran,
Professor of Biophysics,
University of Chicago

In the time allotted, I could abbreviate my talk by pointing out that the ultimate in data reduction and certainly in retrieval is the human brain. I might add, it took 2-billion years to arrive at it. This, in fact, has been the inspiration in our own quest to apply modern techniques, and specifically electron optical techniques, to data reduction and retrieval.

The present electron microscopes work with electrons accelerated to about 100 kV, which have essentially a wave length 100,000 times shorter than that of visible light. Consequently, we already can see, at this time, details of atomic and molecular structure. Now this works both ways. By virtue of having such a short wavelength, we also can reduce, and, despite the rather primitive state of our electromagnetic lenses, we actually can reduce by a factor of 10,000 to 100,000.

Working in our specially equipped laboratories at the University of Chicago, with the generous assistance of the National Aeronautics & Space Administration and the National Institutes of Health, we have been able to combine the unique advantages of superconducting lenses, improved electron sources, and high voltage electron microscopy to achieve resolutions of 2.06 to 4.12 Å in crystalline lattices and point resolutions of 3 to 8 Å in 250 to 350 Å-thick biological specimens. (Figs. 1 and 2)





With a microscope equipped with improved point cathode sources which I developed and which now are used routinely in all the microscopes in our laboratory to provide coherent, bright microbeam illumination, we can demagnify by factors of 10,000 to 100,000 in a single direct imprinting. The miniaturized image is recorded on special light—and electron-sensitive films developed in our laboratory and mounted on electron microscope slides. Whole books can be reduced to the size of a nearly invisible dot, and each slide can contain hundreds of books, which are then read out by light- or electron-optical magnification.

As you can see in the accompanying picture (Fig. 3), prepared with the aid of my coworker Charles Hough and other colleagues at the

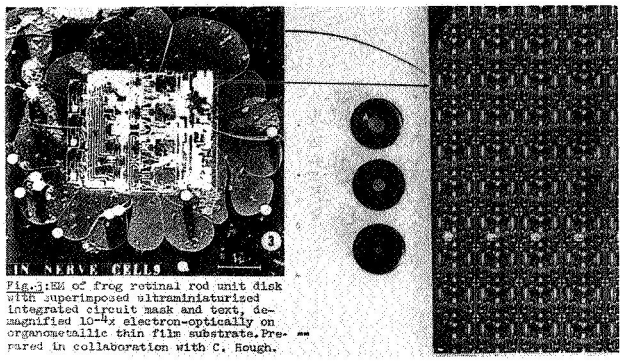
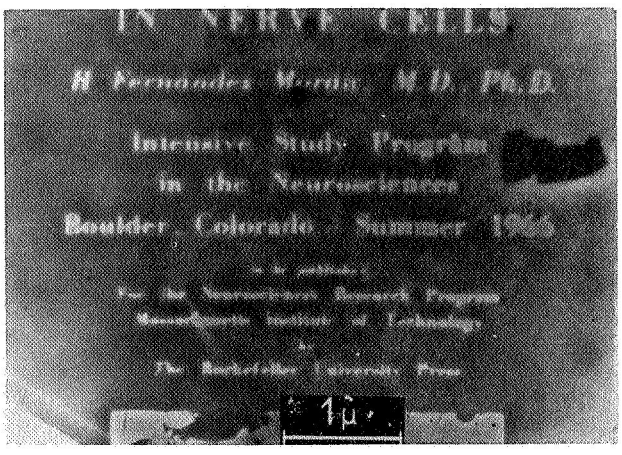


Fig. 3: EM of frog retinal rod unit disk with superimposed ultraminiaturized integrated circuit mask and text, demagnified 10^{-4}x electron-optically on organometallic thin film substrate. Prepared in collaboration with C. Hough.

university, this degree of ultraminiaturization which reduces the letters on a page to 100 Å in size (Fig. 4) allows us to build miniaturized



electronic circuits. The curved line in the center of the micrograph is a size reference point—a human eyelash.

These techniques make it feasible to think of storing the entire miniaturized Library of Congress on a single 8 x 10-in. sheet of paper or on plastic film.

To continue this work, we have installed a closed-cycle, liquid-helium II refrigerator with the expert assistance of Samuel C. Collins of Cryogenics Technology Inc. and his colleagues, Milton Streeter and Richard Osburn.

Now that the system is completely functional, it can continuously operate in the 1.85 to 2.0 K range, and superfluid conditions can be repeatedly obtained in the microscope dewar for from 2 to 4 hr and longer if desired. These superstable lenses, ultrahigh cryogenic vacuum and improved image contrast combined in a single cryoelectron microscope system permit us to demagnify, for example, these cryotrons and integrated circuits by a factor of 10,000 under direct visual control.

Holography also is a very useful tool for information retrieval. In fact, this imaging system—viewing a three-dimensional object without the use of a lens—was first proposed by Dennis Gabor, a Hungarian scientist working with electron microscopes, in 1948. In trying to circumvent the problems created by the electromagnetic lenses, he exposed photographic film to the electron waves from the specimen which was not yet focused.

The development of an improved, coherent electron beam and the laser beam made this type of imaging even more practical.

The beam is divided so that one part lights the object and the other part goes directly to the film.

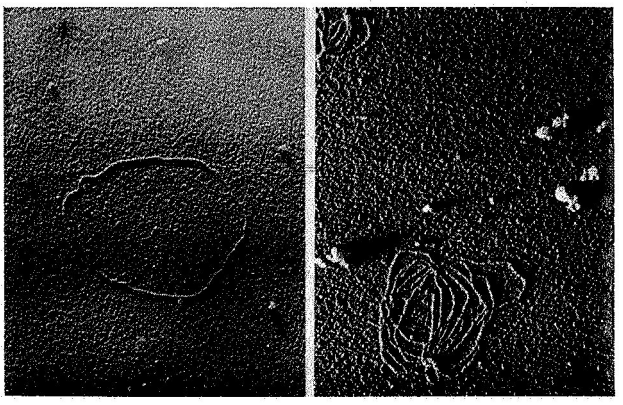
The interference pattern created by the convergence of these two beams on the film contains all the information for 3-D viewing of the object.

When the film is developed, it is viewed with a coherent light source, such as the laser. This provides tremendous possibilities in retrieving information once you have the reference beam. The specimen beam enables you to retrieve just the item you want from a large bank of data.

The ultimate goal, as I pointed out, is an attempt to duplicate the fine structure of the nervous system down to the molecular level. Each of us has on the order of 10^{10} cells in our nervous system. What we are aiming at is to reproduce this degree of ultraminiaturization. I do not mean this in a figurative sense, but in a very real one.

On this chart, which now is old, we have the storage capacity of one of the present-day computers, and the projected trends for the future. With cryo-electronic memories, you are dealing especially with the tunneling devices with structures of only 10 to 30 Å for the active junctions, but they probably will be the large storage and pico-second switching time memories. If we can reach this, I think we might, at least as far as the storage capacity is concerned, approach the human brain.

The next figure (Fig. 5) shows that the ultimate in reliable condensation of data can be found within our 50-trillion-odd cells—



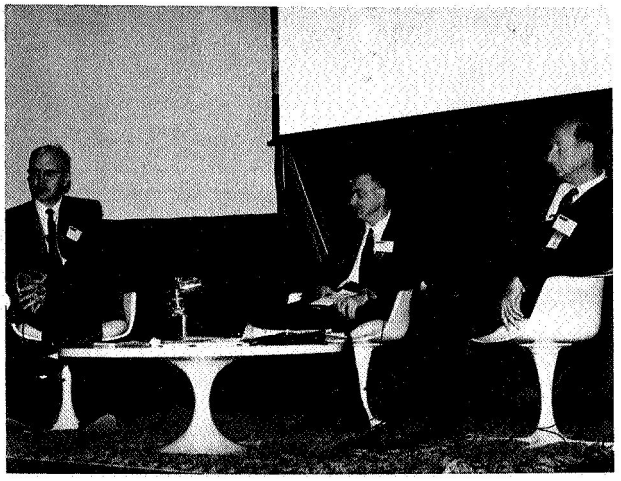
namely DNA, the master molecule of life contained in the chromosomes. Improved instrumentation, preparation techniques and resolving power have already permitted man to directly visualize these tiny structures.

Now we might ask, "Is it possible to modify these structures?" Well, it not only is possible, it is happening, unfortunately, all the time with environmental influences such as radiation, chemical and other agents, *etc*.

With the use of the diamond knife and a "cryo-ultra-microtome" which I invented, we can slice these ribbons of nucleotides and possibly reshape this crucial chain. This, combined with our improved ability to quantitatively predict biological reactions, may free mankind from the burden of its hereditary ailments.

My final presentation will refer to the use of data condensation and retrieval in the context of the new possibilities that have opened up with the use of satellites. It is possible today to make these micro-projectors, or pico-libraries as we call them, in such a size—I hold one here in my hand—as to be conveniently carried.

You can condense a great deal of information and project it at your convenience on a screen or on a suitable surface. Perhaps we'll leave the demonstration of this device to the discussion.



QUESTION: I think we are all a little curious to see what Dr. Moran has there. It looks like a spray gun.

DR. MORAN: The original image—it can be either black-and-white or color—is condensed and then magnified a few thousand times.

This brings me to a very important point, namely that you have the resolution here for use with the electron microscope. Although these photos are all made with a light microscope, the edges are extremely sharp. This edge effect is extraordinary. It is roughly an entire library, and once you have the original, you can make contact prints. If you were to provide these for a given audience, say students, and project them with the possible assistance of a computer for specific data retrieval, you could actually provide intercontinental educational television broadcasting.

The speakers address an audience of millions via satellite. Each student would have his own library, so when he was told to turn to a given page, it would project the image. I mention this merely as an example of the potential already available.

I would like to comment on the electron beam pointer cited by Dr. Rajchman. I am confident that the electron beam, which is much shorter than light waves and can be deflected, has a hitherto unexploited potential. I have been surprised to see how other countries such as Japan and Germany have taken up research in this field, and have used the electron beam for micro-reading. I might add that this is by no means an impractical thing.

A few years ago we celebrated the 25th anniversary of the Electron Microscope Society. The resolution limit of the microscope is about 2 Å. What you can see, you also can duplicate. When you are dealing with this degree of resolution and with the expertise involved, I believe it would be foolish to sell this technique short.

QUESTION: I wonder if someone else on the panel might have some comments.

MR. KILBY: Certainly the type of work that Dr. Moran has talked about has very substantial implications for integrated circuits. Some of the gains we can make there, as Dr. Rajchman pointed out, are diluted by the fact that sooner or later we have to make connections to it. But the potential for still further cost reduction in this area is most attractive.

DR. MORAN: I'm glad the point of connection was brought out. When you are dealing with structures as small as those that I have shown here, you don't establish material connections. You use the pointer, the electron or ion beam, as your connecting media. In other words, you use electron optics to read out your information.

I would like to leave this general concept with you. This very fine beam is literally not more than a hundred angstroms, and it can be deflected by a magnetic or electro-static field at great rapidity. This makes the electron or ion beam a very efficient connector.

Once you have a conceptual advance which represents a "quantum step" jump, what you need to do is to depart from established ways of thinking. Instead of thinking of a mechanical connector which would make a cumbersome structure, you make full use of the potential inherent in the tool that you are employing—the electron beam.

MR. KILBY: I guess I am a little depressed at the thought of trying to connect a few hundred beams simultaneously as a unit, but I realize that it probably could be done.

DR. MORAN: You would use a fly's eye electro-magnetic or electro-static lens as proposed by scientists both in this country and abroad.

They are relatively simple to make. If you take thin metal sheets and perforate them with a million holes, you will have a million lenses. With this system, you can approximate von Neumann's multiplexing concept. Essentially, this means that you would introduce redundancy so the reliability of the whole system is greater than the reliability of any of its parts.

The micro-componentry required by the multiplexing system may be on the order of about 10^{16} to 10^{19} active elements.

DR. RAJCHMAN: I would like to make one remark. I generally agree with Dr. Moran about the fact that electron microscopy and electron beam techniques are things of the future. I want to put one word of caution, however.

When the first memory devices were made, everyone thought that the way to do it was to use an electron beam. It turned out that the very ease with which it is possible to deflect an electron beam also made it difficult to do this in reliable fashion. There were a number of failures. People who tried to deflect beams to such relatively coarse grids as 64 x 64 found it difficult to come back to the same point an hour later. Now I don't want to say there is anything impossible in this, but the facts of history are that this proved to be extremely difficult.

There have been many failures. It was the avoidance of the deflection problem by matrix type memories that really created the computing art. I also think, paradoxically, that because it is more difficult to deflect a light beam, it might be more reliable than the electron beam.

For example, if one were to deflect the light beam by means of acoustic waves, which seems to be a good way of doing it, then the position of the deflection would depend only on the frequency of the wave, and the frequency is the one parameter that is most easy to control. Furthermore, deflection of the entire picture, rather than just the pointer, is really an exciting probability. Now, this could be done with electron beams as well as with light, but at the moment I think it is more difficult.

DR. MORAN: I'm glad Dr. Rajchman pointed this out. I fully agree with him.

The earth's magnetic field, one-half gauss, must be reduced by 10-million times in order to guarantee that a transient magnetic field does not erase your whole picture. A strong increase in magnetic field would erase magnetic tapes.

Fortunately, however, there has been a remarkable breakthrough. We don't speak much of breakthroughs in our field; we talk of "seep throughs"—and this is the way things go. The particular event I'm alluding to is the practical use of cryogenics.

Samuel Collins has played a monumental role in this work. With superconducting shielding, this limitation that Dr. Rajchman referred to—namely the deflection of the beam becoming random, erratic and subject to environmental perturbation—is greatly diminished.

In fact, the persistent current type shielding with superconductors makes possible a great many things, including holography. When Gabor first enunciated the holography idea, he ran across very much the same problems. If you are recording a hologram and a truck goes by, there also goes your hologram. I think these new advances make this approach at least worth looking into.

QUESTION: In approximately the last two months, a number of articles have appeared in the electronics publications specifically attributing remarks to representatives of RCA and Texas Instruments. The context of these remarks was that in microelectronics in the next 10 years there is not likely to be much concentration on new materials developments, except in certain specific areas where the materials have unique interactive effects, such as magneto-optics or magneto-semiconducting materials. Could you give us any more insight into this?

MR. KILBY: I'm not sure that I fully understand the question. Is this on the interactive effects in materials?

QUESTION: The comments were that there's not going to be much in the way of developing new materials, except materials that have novel interactive effects.

MR. KILBY: I see. Well, we are doing a good deal of work in the general field of electro optics where we are interested in optical inputs, optical outputs, true semiconductor devices, and the combinations and prime mutations that you can do with these.

Actually, 10 years ago, when we really began to work on the present monolithic integrated circuit configurations, there was a substantial amount of interest in the Air Force and in the country on the possibility of systematically inventing a series of devices for every electronic requirement. At that time the program was called "molecular electronics." The plan then was to rather very systematically search through all of the existing effects, materials, combinations of effects, and combinations of materials and come up with radically new equipments which would not have any resistors, transistors, or existing elements in them. This proved to be very difficult with the state-of-the-art.

One of the reasons that present-day integrated circuit configurations were off to a fast start was that they offered a systematic approach for bringing some of these functions into the tent. In the process of this rather basic work on inventing new functions, namely interactions, things of that sort were pushed aside, and have not really been exercised very thoroughly anywhere in the industry. Most of the effort has gone into building semiconductor circuits of one sort or another. I think that's about to change, and I think that perhaps there will be considerably increased emphasis in that area in the years to come. There

certainly should be.

DR. RAJCHMAN: I substantially agree with Mr. Kilby. I do think that silicon technology is proving itself to be so good there really is not much sense to try to find another technology to do the same thing. To do other things, such as interaction with light, yes. And it's perfectly true that a lot of research is going on into materials that influence light or can be influenced by light.

QUESTION: Dr. Moran, perhaps you already have answered this and I didn't hear it, but how is that device different from a microfilm camera? What's the size of your image on it?

DR. MORAN: Well, actually, it's a dual purpose device. Right now I was using it as a projector. It could equally well be used as a camera. The answer to your question is that the size of the individual frames can be made much smaller—from a few millimeters to 1/1000 of a millimeter. If you replaced the imaging elements with a specially constructed, high-resolution image intensifier, you could put it on television. What this gives you, both in the projection and recording modes, is essentially an unprecedented density of information recording and retrieval. A good picture, such as those we saw on the moon landing, contains 10^7 to 10^9 bits. These are very good pictures.

Consider that with our present technology without using any novel things you can put 10^9 bits in a frame the size of 1 x 1 mm. With a little more effort, perhaps even 0.1 x 0.1 mm could be achieved. This considerably enhances the information storage capacity. By the same token, the retrieval is facilitated because once you have one of these films, you can scan it much more rapidly. So this type of approach is bound to be pursued in its many variants.

As I pointed out at the National Academy of Sciences meeting some 4 yr ago ("Biology and the Exploration of Mars, 1966," National Academy of Sciences, pp. 414-425 and 503-505), one of the basic problems in future space exploration would be the limitation of information retrieved to the order of 10^9 bits. This limit on the bits obtainable is inherent in the telemetry parameters. Such restrictions dictate the design of any type of system for the detection of extra-terrestrial life.

Condensing the information obtained during a given mission by factors of 1,000 to 50,000 would increase this limit by several orders of magnitude. These images could then be printed directly onto reels of special thin tape by demagnification electron microscopy, put in a bobbin a few cubic centimeters in size and guided back to earth. Use of such "space courier pigeons" is not advanced science fiction thinking. It is a very real possibility which we are currently exploring to utilize the advantages of transferring information *in toto* rather than by telemetry.

QUESTION: I wonder whether somebody on the panel could comment on the electron beam versus the laser beam. Laser has a penetration that's a range in material of about a few hundred angstroms, and electron beams, in order to get fine lines, have to have relatively high energies, near 100 kV. Now 100-kV electrons penetrate, I would say, about 25 microns in most materials, so the microns would get a lot of scattering inside of the material. What effect does it have on the actual spot size on material that we are recording on?

DR. MORAN: The figures you are quoting are very optimistic. An electron beam, in order to give you a good definition at 100 kV, really doesn't penetrate much more than one tenth of a micron before you get scatter effects. When you go to high energies—200 kV and, as some French, Japanese, and American scientists are doing, 1-million volts—you can go from one to a few microns.

The basic advantage in the electron beam is its shorter wave length. There the laser beam is limited simply by considerations of wavelength.

I do not foresee that there is any exclusion between the two methods. In fact, like all good things, you have a good mix between them. This possibility is particularly attractive when you come to holography. When Gabor introduced it, holography was not practical. We did not have a coherent light to play it back.

With the advent of lasers, it became possible to use these new sources to reconstruct the images. It is in this cooperative role that I see lasers and electron beams interacting very fruitfully.

QUESTION: I would like to address this question to Dr. Moran. With the device that you demonstrated today, is this now commercially available or is it still in the test stages. If it is commercially available can you give us any idea of the price range of something like that?

DR. MORAN: First of all, this is strictly a developmental project carried out in our laboratory with the specifications of the NASA and NIH research programs in mind. The basic ideas go back to my work at the Nobel Institute of Physics in Stockholm nearly two decades ago and at the Venezualan Institute for Brain Research at Caracas in the early 1950s.

The first instrument that we built had a

rather interesting price range. The light was a $1 flashlight, and the total development didn't go much higher than a few hundred dollars at the most. Even the more sophisticated ones do not run much higher.

Someone has suggested that I look into the commercial aspects of it, but at present, we are still working on complete development of the system. I do, however, feel that the time is nearing when it could be commercially available.

QUESTION: In the trend toward microminiaturization customization, who will provide the interface between the producer of the semiconductor and the user? How will this be facilitated? Have you given much thought to this?

MR. KILBY: Yes, we have given a good deal of thought to it, but I'm not sure that we have come up with a single answer. However, we have begun to develop a number of programs. By this I don't mean just computer programs, but activities of all sorts, to begin to establish the kinds of interfaces that will be required for these custom circuit configurations. They are quite different. Our present interface usually consists of printing a few hundred thousand data sheets and giving them to a few hundred field sales engineers and letting them carry them around to see who wants to buy some. The new interfaces will be much more technical in nature, and presumably will be on an engineer-to-engineer basis between the semiconductor companies and the users.

DR. MORAN: I would like to comment on this. Speaking of interfaces, we are particularly indebted in our life to these two gentlemen and the companies they represent. The point I want to make is that one of the ideal interfaces is the university because this is where you really can interact and push forward the frontiers. In the case of RCA, it was one of the great pioneers in our field. One of the men involved in this early work was James Hillier, now vice president for research and engineering at RCA, who made high resolution microscopy not only possible, but also practical. The development dates back to his classical work in 1948.

As regards Mr. Kilby, I can name any number of devices where the distinct interface has been mediated through colleges and universities with the cooperation of Texas Instruments.

QUESTION: Dr. Moran, on the slide that Dr. Rajchman had up there for the cost per bit versus the size of the memory, in terms of your suggested electron microscope memory, would you care to postulate that it could be reached reasonably within your concept of the memory itself?

DR. MORAN: Would you kindly repeat the last sentence?

QUESTION: What would you say that the cost per bit, and the size of the memory would be on that slide Dr. Rajchman had up there for your electron microscope memory?

DR. MORAN: That's a good question. First of all, I'm not responsible for that chart, and, in fact, the chart is several years old. I think I got it from one of the technical journals. I wouldn't venture to give you a figure because this is purely developmental, and as you know, it took integrated circuits a number of years to go from the laboratory to the industry. But if I may "guesstimate" here's the way I would go about it.

I would say that it could come about, providing there is enough interest and competition, not necessarily at the industrial level, but among laboratories. That's a greater incentive to progress. Providing it is forthcoming and there is enough vision to carry out programs that are not on a one or five year basis, but more on a 10-yr basis, then it's conceivable. I am not saying it is possible, but it's conceivable that the cost per bit with electronic devices would be considerably lower.

Dr. Rajchman pointed out that the initial attempts made, using electron optics, were in a scanning mode. I always am reminded of the monks in the Middle Ages writing out their beautiful manuscripts, and doing a commendable job, but getting writer's cramp in the process. By the same token, with electro optics, using the whole picture and the fly's eye approach, one could get purity of recording films and resultant reproducibility and reduce the nucleation factors which were very serious in the early attempts. You might conceive of making these memory banks at one stroke—and that would mean 10^6 to roughly 10^9 integrated elements per slide. If this proves to be the case, then the economics goes down. That's the best I can think of at the present time.

I would like to point out, however, that we're not alone. I was amazed at the tremendous amount of interest—much greater than anything I've seen before—that was being put into industry in other countries like Germany and Japan. Many electron microscopists are being attracted from their study of biological material to ultraminiaturization. In this country, we have two things working in our favor. One of them is that we have the largest electron microscope group in the world. The

second is that we have a distinct lead in cryogenics. If these two factors are put together, you can foresee very significant reductions in cost.

DR. RAJCHMAN: I drew the particular graph that Professor Moran showed. It turns out that it shows capacity versus speed—not cost if you will remember the coordinates. Secondly, I would venture to say that before we get to the super electronically made memories that the optical memories probably will be the next step. I think we'll reach costs to the order of 10^{-4} to 10^{-5} dollars per bit.

DR. MORAN: Here's a formula that might interest Dr. Rajchman. It was stimulated by an interesting statement derived from L. Brillouin* and made by Robert Heidenreich of Bell Telephone Laboratories**: "The information ΔI obtained in measuring a distance ΔL in a domain L is given by

$$\Delta I = k \ln \frac{L}{\Delta L}$$

where k is the Boltzmann constant."

Heidenreich states: "Any distance can be measured directly if enough money and effort are expended to supply the negentropy that must be traded for information."

At one of the last international congresses, it was therefore facetiously remarked that a good yardstick would be to trade one dollar for each volt, which, of course, brings us to the megabuck range when dealing with megavolts.

*"Science and Information Theory," Academic Press, New York, 1956.

**"Fundamentals of Transmission Electron Microscopy," Interscience Press, London, 1964, p. 11.